



This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

- + *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.
- + *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.
- + *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.
- + *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at <http://books.google.com/>

HC 2LY2 2

8. A. 293





A TEXT-BOOK
of
PATHOLOGY

BY

ALFRED STENGEL, M. D., Sc. D.

Professor of Medicine, University of Pennsylvania; Physician to the Pennsylvania
and to the University Hospitals

AND

HERBERT FOX, M. D.

Director of the Pepper Laboratory of Clinical Medicine, University of Pennsylvania;
Pathologist to the Philadelphia Zoological Garden

SIXTH EDITION, RESET

WITH 468 TEXT ILLUSTRATIONS, MANY
IN COLORS, AND 15 COLORED PLATES

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

1915

13127831 5.40

Copyright, 1898, by W. B. Saunders. Revised, reprinted, and recopyrighted March, 1899. Reprinted August, 1899; November, 1899. Revised, reprinted, and recopyrighted October, 1900. Reprinted July, 1901; September, 1902. Revised, reprinted, and recopyrighted July, 1903. Reprinted March, 1905. Revised, reprinted, and recopyrighted September, 1906. Reprinted November, 1907, August, 1909, August, 1910, July, 1911, and June, 1912. Revised, entirely reset, reprinted, and recopyrighted August, 1915

COPYRIGHT, 1915, BY W. B. SAUNDERS COMPANY

PRINTED IN AMERICA

PRESS OF
W. B. SAUNDERS COMPANY
PHILADELPHIA

PREFACE TO THE SIXTH EDITION

IN the preparation of the present (the sixth) edition of the Text-book of Pathology I am fortunate in having the co-operation of Dr. Herbert Fox, whose active interest in general and comparative pathology and in clinical pathology peculiarly fit him for collaboration in a book designed especially for the needs of students and practitioners preparing for or engaged in the work of practical medicine. The book hereafter will appear under our joint authorship, each having contributed largely to the present edition.

Extensive revision has been found necessary to bring the work fully to date. In the first portions, devoted to general pathology, the sections on Inflammation, Retrogressive Processes, Disorders of Nutrition and Metabolism, General Etiology, and Diseases due to Bacteria have been very largely recast or almost wholly rewritten. A new section on Transmissible Diseases has been added; the Terata have been incorporated with a brief synoptical chapter on Teratology; the Glands of Internal Secretion and their pathology have been made the subject of a separate chapter; and new sections on the pathology of the eye, ear, and skin, brief and general in scope, but, we hope, sufficient for a work of this character, have been added. It has seemed best to us to omit the chapter on Technic, which formed a part of previous editions, because the necessary brevity of such a chapter deprives it of practical usefulness. Special works on technic should be consulted by the student and laboratory worker. The chapters on Diseases of the Nervous System occupied a disproportionately large part of previous editions and have, therefore, been curtailed. Numerous revisions have been made in other sections and chapters of special pathology where advances in knowledge have required such alterations. Many new illustrations—upward of 100 in black and white or color—have been added, and by reason of the liberal policy of the publishers, to whom our thanks are due, the whole work has been reset and appears in a new and greatly improved form.

ALFRED STENGEL.

PHILADELPHIA, PA., *August*, 1915.

CONTENTS

PART I—GENERAL PATHOLOGY

CHAPTER I		PAGE
THE ETIOLOGY OF DISEASE		19
Pathological Disposition, 20—Traumatism, 24—Physical Conditions, 25		
—Poisons, 29—Vegetable and Animal Parasites, 37.		
CHAPTER II		
DISORDERS OF NUTRITION AND METABOLISM		39
Food, 39—Diminished Supply of Food, 39—Increased Supply of Food, 40		
—Metabolism of Fat, 40—Excessive Tissue Destruction, 40—Acid Intoxi-		
cation, 42—Disorders of Protein Metabolism, 44—Disorders of Purin		
Metabolism, 45—Gout, 46—Diseases of Carbohydrate Metabolism, 47—		
Diabetes Mellitus, 49—Fever, 53.		
CHAPTER III		
DISTURBANCES OF THE CIRCULATION OF THE BLOOD		56
General Disturbances, 56—Local Anemia, 58—Local Hyperemia, 59—		
Hemorrhage, 60—Embolism, 64—Infarction, 66—Thrombosis, 67—Edema,		
72.		
CHAPTER IV		
RETROGRESSIVE PROCESSES		76
Atrophy, 76—So-called Infiltrations and Degenerations, 78—Cloudy		
Swelling, 78—Fatty Infiltration, 80—Fatty Degeneration, 82—Albuminoid		
Degenerations, 85—Hyaline Degeneration, 85—Mucoid Degeneration, 88—		
Colloid Degeneration, 90—Amyloid Infiltration, 91—Glycogenic Infiltration,		
94—Dropsical Infiltration, 95—Calcification, 96—Ossification, 98—Uratic		
Infiltration, 98—Pigmentation, 99—Necrosis, 105—Coagulation Necrosis,		
107—Liquefaction Necrosis, 109—Caseation, 110—Fat Necrosis, 111—		
Gangrene, 112—General Pathology of Cellular Necrosis, 114—Alterations		
in Cell Nuclei in Necrosis, 114—Alterations in Form of Cells in Necrosis,		
114—Altered Karyokinesis in Necrotic Cells, 115—Postmortem Altera-		
tions, 115.		
CHAPTER V		
INFLAMMATION AND REGENERATION		117
Inflammation, 117—Regeneration, 149—Metaplasia, 155.		
CHAPTER VI		
PROGRESSIVE TISSUE CHANGES		157
Hypertrophy, 157—Tumors, 158.		
Connective Tissue Tumors, 169—Fibroma, 169—Myxoma, 173—Lipoma,		
174—Xanthoma, 175—Chondroma, 176—Osteoma, 179.		

Angiomata, 181—**Lymphangioma**, 181—**Hemangioma**, 182—**Lymphadenoma**, 184—**Sarcoma**, 189—**Spindle-celled Sarcoma**, 192—**Round-celled Sarcoma**, 193—**Giant-celled Sarcoma**, 195—**Melanosarcoma**, 197—**Mixed Tumors**, 198—**Mycosis Fungoides**, 199—**Angiosarcoma**, 200—**Cylindroma**, 202—**Endothelioma**, 203—**Psammoma**, 204.

Tumors from Nerve Tissues, 204—**Glioma**, 205—**Glioma Ganglionare**, 207—**Neuroma**, 208—**Leiomyoma**, 209—**Rhabdomyoma**, 211.

Epithelial Tumors, 212—**Papilloma**, 212—**Adenoma**, 215—**Carcinoma**, 219—**Epithelioma**, 227—**Glandular Carcinoma**, 229—**Special Forms of Cancer**, 230—**Cysts**, 231—**Epithelial Cysts**, 232.

CHAPTER VII

TERATOLOGY..... 235

Teratomata, 235—**Dermoid Cyst**, 236—**Other Teratoid Tumors**, 236—**Synecioma Malignum**, 238—**Terața or Monsters**, 239.

CHAPTER VIII

BACTERIA, THEIR NATURE AND ACTION..... 241

Classification, 241—**Morphology**, 243—**Biology**, 245—**Functions and Products of Bacteria**, 247—**Products in Culture-medium**, 250—**Local Effects of Bacteria**, 251—**Effect of Toxic Products of Bacteria**, 251—**Immunity**, 255.

CHAPTER IX

DISEASES DUE TO BACTERIA..... 273

Diseases Due to Cocci, 273—**Suppurative Diseases**, 273—**Gonorrhea**, 278—**Croupous Pneumonia**, 280—**Other Forms of Pneumonia**, 283.

Diseases Due to Bacillary Forms, 285—**Diphtheria**, 285—**Typhoid Fever**, 289—**Bacillus Coli Communis**, 295—**Dysentery Bacillus**, 297—**Influenza**, 298—**Bordet-Gengou Bacillus of Whooping-cough**, 299—**Bubonic Plague**, 300—**Soft Chancre**, 302—**Malta Fever**, 303—**Rhinoscleroma**, 303—**Glanders**, 304—**Tetanus**, 306—**Anthrax**, 308—**Malignant Edema**, 311—**Infectious Emphysema**, 312—**Tuberculosis**, 313—**Pseudotuberculosis**, 324—**Fowl-tuberculosis**, 325—**Leprosy**, 326—**Bacterium Mucosum Capsulatum Group**, 329.

Diseases Due to Spirilla, 330—**Cholera**, 330—**Organisms Resembling the Cholera Vibrio**, 333.

Diseases Due to Spirochetes, 334—**Syphilis**, 334—**Relapsing Fever**, 339—**Vincent's Angina**, 340—**Frambesia or Yaws**, 341.

Diseases Due to Higher Bacteria, 341—**Actinomycosis**, 341—**Mycetoma**, 346—**Thrush**, 347—**Saccharomycosis or Blastomycosis**, 348.

Other Bacteria Not Causing Specific Infection, 349—**The Hemorrhagic Diseases**, 349—**Proteus Infection**, 350.

Infectious Diseases Whose Cause is Not Certainly Known. Filterable Viruses, 351—**Yellow Fever**, 351—**Measles**, 352—**Scarlet Fever**, 353—**Mumps**, 354—**Variola and Vaccinia**, 354—**Varicella**, 355—**Typhus Fever**, 355—**Rabies**, 356—**Rheumatism**, 358—**Beriberi**, 359—**Pellagra**, 360—**Dengue**, 360—**Poliomyelitis**, 361—**Foot-and-mouth Disease**, 362—**Trachoma**, 362—**Rocky Mountain Fever**, 362—**Chlamydozoa**, 363.

CHAPTER X

ANIMAL PARASITES AND DISEASES CAUSED BY THEM..... 364

Protozoa, 364—**Rhizopoda**, 364—**Entamoeba Histolytica**, 364—**Entamoeba Coli**, 366—**Other Amebæ**, 366—**Mastigophora**, 366—**Cercomonas**

Hominis, 366—*Cercomonas Coli Hominis*, 367—*Trichomonas Intestinalis*, 367—*Trichomonas Vaginalis*, 368—Other Forms of *Trichomonas*, 368—*Lambia Intestinalis*, 368—*Trypanosoma*, 369—*Hemosporidia*, 372—Parasites of Malaria, 372—*Coccidia*, 377—*Coccidium Cuniculi*, 377—*Sarcosporidia*, 378—*Infusoria*, 379—*Balantidium Coli*, 379—Animal Parasites and *Molluscum Contagiosum*, 379.

Vermes, 380—Trematodes, or Fluke-worms, 380—*Fasciola Hepatica*, 380—*Dicrocoelium Lanceatum*, 381—*Opisthorchis Felineus*, 382—*Opisthorchis Sinensis*, 382—*Schistosomum Hæmatobium*, 382—*Schistosomum Japonicum*, 383—*Paragonimus Westermanii*, 383—Other Fluke-worms, 384.

Cestodes, or Tapeworms, 384—*Tænia Solium*, 386—*Tænia Saginata*, 388—*Hymenolepis Nana*, 389—*Hymenolepis Diminuta*, 389—*Dipylidium Caninum*, 390—*Davainea Madagascariensis*, 390—*Tænia Echinococcus*, 390—*Dibothriocephalus Latus*, 393—*Dibothriocephalus Cordatus*, 394—*Bothriocephalus Mansonii*, 394—*Diplogonoporus Grandis*, 394.

Nematodes, or Round Worms, 395—*Ascaris Lumbricoides*, 395—*Ascaris Canis*, 395—*Oxyuris Vermicularis*, 396—*Trichinella Spiralis*, 396—*Ankylostoma Duodenale*, 397—*Necator Americanus*, 399—*Strongyloides Intestinalis*, 400—*Trichocephalus Trichiuris*, 401—*Filaria Medinensis*, 401—*Filaria Bancrofti*, 402—Other Forms of *Filaria*, 404—*Echinorhynchus Gigas*, 404—*Eustrongylus Gigas*, 405—*Strongylus Apri*, 405—*Strongylus Subtilis*, 405—*Annelides*, 405—*Arthropoda*, 405—*Linguatula Rhinaria*, 406—*Porocephalus Constrictus*, 406—*Myiasis*, 406.

CHAPTER XI

THE METHODS OF TRANSMISSION OF THE COMMUNICABLE DISEASES. 407
Direct Infection, 408—Indirect Transmission, 409.

PART II—SPECIAL PATHOLOGY

CHAPTER I

DISEASES OF THE BLOOD. 412

Anatomy, 412—Blood Formation, 419—Pathological Changes in the Red Corpuscles, 420—Pathological Changes in the Leukocytes, 422—Pathological Changes in the Plasma, 423—Plethora, 424—Oligemia, 424—Hydremia and Anhydremia, 425—Lipemia, 425—Melanemia, 426—Hemocytolysis; Hemoglobinemia, 426—Polycythemia, 427—Leukocytosis, 428—Leukopenia, 430—Anemia, 431—The Secondary Anemias, 431—The Primary Anemias, 433—Chlorosis, 433—Progressive Pernicious Anemia, 435—Aplastic Anemia, 437—Hemolytic Ictero-anemia, 438—Leukemia, 438—Hodgkin's Disease, 441—Pseudoleukemia Infantum, 441—Foreign Bodies and Parasites, 442.

CHAPTER II

DISEASES OF THE LYMPHATIC TISSUES. 443

Spleen, 443—Abnormal Development and Situation, 444—Circulatory Disturbances, 444—Inflammation, 445—Atrophy and Degenerations, 448—Leukemia and Hodgkin's Disease, 449—Tumors and Parasites, 449—Infectious Diseases, 450.

	PAGE
Lymphatic Glands , 450—Atrophy, 452—Hypertrophy, 452—Status Lymphaticus, 452—Degenerations, 453—Inflammation, 454—Infectious Diseases, 456—Leukemia and Hodgkin's Disease, 459—Tumors, 461.	
Bone-marrow , 462—Degenerations, 463—Atrophy, 464—Hypertrophy, 464—Inflammation, 465—Tumors, 466.	

CHAPTER III

DISEASES OF THE CIRCULATORY SYSTEM	467
---	-----

Heart, 467—Congenital Diseases and Deformities, 468—Circulatory Disturbances, 471—*Endocardium*, 472—Inflammation, 473—*Myocardium*, 481—Degenerations, 481—Inflammation, 486—Hypoplasia and Atrophy, 492—Hypertrophy and Dilatation, 494—Aneurysm, 496—Wounds and Rupture of Heart, 497—Infectious Diseases, 497—New Growths and Parasites, 497—*Pericardium*, 498—Circulatory Disturbances, 498—Inflammation, 498—Infectious Diseases, 502—Tumors and Parasites, 502—Pneumo-pericardium, 503.

Arteries, 503—Congenital Defects, 503—Hypertrophy, 503—Atrophy, 504—Degenerations, 504—Inflammation, 505—Infectious Diseases, 511—Aneurysm, 511.

Veins, 517—Circulatory Disturbances, 517—Degenerations, 518—Inflammation, 518—Dilatation, 519—Tumors, 520—Infectious Diseases, 520.

Lymphatic Channels, 521—Inflammation, 521—Dilatation, 521—Infectious Diseases, 522—Tumors, 522—Parasites, 523.

Thoracic Duct, 523.

CHAPTER IV

DISEASES OF THE RESPIRATORY SYSTEM	524
---	-----

Nasal Cavities, 524—Congenital Abnormalities, 524—Circulatory Disturbances, 524—Inflammations, 525—Infectious Diseases, 525—Tumors, 526—Parasites and Foreign Bodies, 526.

Larynx, 526—Congenital Abnormalities, 526—Circulatory Disturbances, 527—Inflammations, 527—Infectious Diseases, 528—Tumors, 529—Parasites and Foreign Bodies, 530.

Trachea, 530—Malformations, 530—Circulatory Disturbances, 531—Inflammations, 531—Infectious Diseases, 531—Tumors, 531.

Bronchi, 531—Congenital Malformations, 532—Circulatory Disturbances, 532—Inflammations, 532—Stenosis and Obstruction, 534—Dilatation, 535—Infectious Diseases, 536—Tumors, 536—Parasites and Foreign Bodies, 537.

Lungs, 537—Congenital Defects, 538—Circulatory Disturbances, 538—Hypertrophy and Atrophy, 543—Emphysema, 543—Atelectasis, 546—Inflammation or Pneumonia, 548—Gangrene, 565—Infectious Diseases, 566 Syphilis, 578—Glanders, 579—Actinomycosis, 580—Tumors, 580—Parasites, 584.

Pleura, 585—Inflammation, 586—Infectious Diseases, 591—Tumors and Parasites, 592.

CHAPTER V

DISEASES OF THE GASTRO-INTESTINAL TRACT	594
--	-----

Mouth, 594—Congenital Abnormalities, 594—Circulatory Disturbances, 594—Inflammation, 594—Atrophy and Degenerations, 598—Infectious Diseases, 598—Tumors, 600.

Teeth, 601.

Pharynx and Tonsils, 602—Circulatory Disturbances, 602—Inflammations, 602—Pressure Necrosis, 606—Infectious Diseases, 606—Tumors, 608.

Salivary Glands, 608.

Esophagus, 609—Congenital Defects, 609—Circulatory Disturbances, 609—Inflammations, 610—Stenosis, 610—Dilatation, 611—Perforation and Rupture, 611—Infectious Diseases, 612—Tumors, 612.

Stomach, 613—Congenital Defects, 613—Circulatory Disturbances, 613—Inflammation, 614—Gastric Ulcer, 617—Atrophy and Degenerations, 620—Alterations in Position and Size, 621—Infectious Diseases, 622—Tumors, 622.

Intestines, 626—Congenital and Acquired Abnormalities, 626—Intestinal Obstruction, 629—Prolapse of Rectum, 630—Atrophy and Degenerations, 631—Circulatory Disturbances, 631—Inflammations, 633—Inflammations of Special Parts, 635—Infectious Diseases, 639—Tumors, 648—Parasites, 651—Intestinal Rupture and Foreign Bodies, 652.

Liver, 653—Malformations and Changes of Position, 653—Circulatory Disturbances, 654—Atrophy and Degenerations, 657—Rupture of the Liver, 671—Infectious Diseases, 671—Tumors, 673—Parasites, 677.

Biliary Ducts and Gall-Bladder, 678—Inflammations, 678—Stenosis and Dilatation, 680—Gall-stones; Cholelithiasis, 681—Tumors, 683—Jaundice, 683.

Pancreas, 685—Congenital Abnormalities, 685—Circulatory Disturbances, 685—Atrophy and Degenerations, 685—Inflammations, 687—Infectious Diseases, 689—Tumors, 689—Pancreatic Duct, 690.

Peritoneum, 691—Congenital Abnormalities, 691—Circulatory Disturbances, 691—Inflammations, 693—Infectious Diseases, 696—Tumors, 698—Parasites, 698.

CHAPTER VI

DISEASES OF THE DUCTLESS GLANDS 699

Thyroid Gland, 699—Congenital Defects, 699—Disturbances of Circulation, 699—Inflammations, 700—Struma or Goiter, 700—Infectious Diseases, 705—Tumors and Parasites, 705—General Results of Thyroid Disease, 705.

Suprarenal Bodies, 708—Congenital Anomalies, 709—Degenerations, 709—Infectious Diseases, 709—Circulatory Disturbances, 710—Inflammation, 711—Tumors, 711.

Thymus Gland, 711.

Pituitary Body, or Hypophysis Cerebri, 712.

Pineal Gland, or Epiphysis Cerebri, 715.

CHAPTER VII

DISEASES OF THE URINARY ORGANS 717

Kidneys, 717—Congenital Anomalies, 717—Changes of Position, 717—Circulatory Disturbances, 718—Inflammations, 720—Nephritis, 720—Acute Parenchymatous Nephritis; Bright's Disease, 722—Acute Interstitial Nephritis, 724—Chronic Nephritis, 726—Chronic Parenchymatous Nephritis, 726—Chronic Interstitial Nephritis, 729—Atrophy and Hypertrophy, 737—Degenerations, 737—Concretions in Uriniferous Tubules, 740—Infectious Diseases, 741—Tumors, 741—Parasites, 747.

Pelvis of Kidney and Ureter, 748—Congenital and Acquired Malformations, 748—Calculus, 749—Inflammation, 749—Infectious Diseases, 750—Tumors, 751—Parasites, 751.

	PAGE
Urinary Bladder , 752—Malformations, 752—Changes of Position, 752—Rupture, 753—Circulatory Disturbances, 753—Inflammation, 753—Infectious Diseases, 755—Calculi and Foreign Bodies, 755—Tumors, 757—Abnormal Conditions of Urine, 758—Chemical Changes and Sediments, 764.	
Urethra , 766—Inflammations, 767—Injuries, 770—Infectious Diseases, 770—Tumors, 770.	

CHAPTER VIII

DISEASES OF THE REPRODUCTIVE ORGANS.....	771
--	-----

Uterus, 771—Congenital Abnormalities, 771—Alterations of Position, 772—Stenosis, Dilatation, and Rupture, 775—Circulatory Disturbances, 775—Inflammations, 777—Infectious Diseases, 780—Atrophy and Degeneration, 783—Hypertrophy and Hyperplasia, 783—Tumors, 784—Parasites, 790.

Ovaries, 790—Congenital Abnormalities, 790—Changes in Position, 790—Circulatory Disturbances, 791—Inflammation, 791—Infectious Diseases, 792—Tumors, 792—Cysts of Parovarium, 796—Cysts of Kobelt, 797.

Fallopian Tubes, 797—Congenital Abnormalities, 797—Changes of Position, 797—Stenosis, 798—Dilatation, 798—Circulatory Disturbances, 798—Inflammations, 799—Infectious Diseases, 801—Parametrium, 803—Extra-uterine Pregnancy, 803.

Vagina, 805—Prolapse of Walls, 805—Stenosis, 805—Wounds and Fistulae, 805—Circulatory Disturbances, 806—Inflammations, 806—Infectious Diseases, 807—Tumors, 807.

Vulva, 807—Wounds, 808—Circulatory Disturbances, 808—Inflammation, 808—Infectious Diseases, 809—Tumors, 809.

Decidua, Placenta, and Fetal Membranes, 810—Abnormalities of Development, 810—Circulatory Disturbances, 811—Inflammation, 811—Infectious Diseases, 812—Hyperplasia, 812.

Penis and Scrotum, 814—Congenital Abnormalities, 814—Inflammation, 814—Infectious Diseases, 815—Tumors, 815—Injuries, 816.

Testicles, 816—Anatomical and Physiological Considerations, 816—Congenital Abnormalities, 816—Atrophy and Hypertrophy, 817—Degenerations, 817—Circulatory Disturbances, 818—Inflammation, 818—Infectious Diseases, 821—Tumors, 822—Parasites, 824.

Prostate Gland, 824—Inflammation, 824—Atrophy and Degeneration, 824—Concretions, 825—Infectious Diseases, 825—Hypertrophy and Tumors, 825.

Cowper's Glands, 828.

Seminal Vesicles, 828.

Mammary Glands, 829—Congenital Abnormalities, 829—Circulatory Disturbances, 829—Inflammations, 829—Atrophy and Hypertrophy, 830—Degenerations, 831—Infectious Diseases, 831—Tumors, 831.

CHAPTER IX

DISEASES OF THE BONES.....	836
----------------------------	-----

Disorders of Development, 836—Rickets, 837—Regeneration, 839—Circulatory Disturbances, 841—Inflammations, 842—Degenerative Conditions, 846—Hypoplasia and Atrophy, 847—Infectious Diseases, 849—Tumors, 853.

CHAPTER X

DISEASES OF THE JOINTS.....	855
-----------------------------	-----

Distortions, 855—Circulatory Disturbances, 856—Inflammations, 856—Infectious Diseases, 860—Tumors, 862—Tendon-sheaths and Bursae, 862.

CHAPTER XI

DISEASES OF THE VOLUNTARY MUSCLES	PAGE 863
Hypertrophy, 863—Circulatory Disturbances, 863—Inflammations, 864	
—Atrophy and Degenerations, 866—Infectious Diseases, 869—Tumors and Parasites 869.	

CHAPTER XII

DISEASES OF THE BRAIN AND ITS MEMBRANES	870
Dura Mater , 870—Circulatory Disturbances, 870—Infectious Diseases, 872—Tumors, 872—Cysts, 873.	
Pia-arachnoid , 873—Circulatory Disturbances, 874—Inflammation, 874—Infectious Diseases, 878—Tumors, 880.	
Brain , 882—Development and Anatomy, 882—Postmortem Degenerative Conditions, 886—Congenital Abnormalities, 887—General Pathological Anatomy of Nervous System, 891—Blood-vessels, 900—Circulatory Disturbances, 902—Inflammation, 910—Injuries to Central Nervous System, 917—Infectious Diseases, 918—Tumors, 919—Choroid Plexus, 922.	

CHAPTER XIII

DISEASES OF SPINAL CORD AND ITS MEMBRANES	928
Dura Mater , 928.	
Pia-arachnoid , 929—Circulatory Disturbances, 929—Degenerations, 929—Inflammations, 930—Infectious Diseases, 930.	
Cord , 931—Anatomy, 931—Congenital Abnormalities, 933—Hydromyelia and Syringomyelia, 934—Circulatory Disturbances, 936—Inflammation, 938—Primary Degenerations, 943—Secondary Degenerations, 953—Tumors, 957.	

CHAPTER XIV

DISEASES OF THE PERIPHERAL NERVOUS SYSTEM	958
Ganglia of Cranial and Spinal Nerves , 958.	
Nerves , 958—Circulatory Disturbances, 958—Regeneration after Injury, 959—Inflammations, 960—Infectious Diseases, 962—Tumors, 963.	

CHAPTER XV

THE EYE	964
Anatomy, 964—Congenital Abnormalities, 965—Conjunctiva, 965—Lachrymal Organs, 970—Cornea, 970—Sclera, 972—Crystalline Lens, 973—Vitreous Humor, 974—Iris, 974—Ciliary Body, 976—Choroid, 977—Retina, 978—Sympathetic Ophthalmitis, 980—Glaucoma, 980—Optic Nerve, 981—Orbit, 983—Lids, 983.	

CHAPTER XVI

THE EAR	984
Anatomy, 984—Congenital Defects, 985—External Ear, 985—Tympanic Membrane, 986—Tumors of External Ear, 986—Middle Ear, 987—Eustachian Tube, 989—Internal Ear, 989.	

CHAPTER XVII

THE SKIN	990
Anatomy, 990—Congenital Abnormalities, 991—Atrophy, Hypertrophy, and Degenerations, 991—Variations in Pigmentations, 993—Circulatory Disturbances, 993—Inflammation (Dermatitis), 994—Specific Inflammations, 1002—Tumors, 1005.	
Structures Within the Skin, 1006—Sebaceous Glands, 1006—Sweat-glands, 1007—Hair, 1008—Nails, 1008.	

INDEX	1009
--------------------	------

A TEXT-BOOK OF PATHOLOGY

PART I

GENERAL PATHOLOGY

PATHOLOGY is the science that deals with disease in all its aspects. It includes the study of the causes, the manifestations, and the results of disease.

Three important subdivisions of the study of pathology are recognized, viz., *etiology*, or the study of the causes of disease; *morbid or pathological anatomy*, the study of the gross and microscopical structural changes in disease; and *morbid or pathological physiology*, the study of disturbances of function. In the latter group is included *pathological chemistry*, as morbid chemical action and its results are the outcome of disturbed function.

Pathology may be divided into *general* and *special* pathology. The former treats of causes of disease and pathological processes irrespective of any individual part; the latter deals with the causes or processes in individual diseases, organs, or parts.

Disease itself is not a separate entity, but may be defined as abnormality in structure, in function, or in both combined. It is doubtful whether alteration of function can occur without some alteration in structure, but it frequently happens that functional disturbances are present though no structural alterations are discoverable even by the most precise methods of investigation.

It is obvious from the foregoing that it is impossible to define sharply either disease or health. Health, or fully harmonious action of all physical and physiological units, is subject to the same laws of mode and mean as any other group of varying but comparable units, and as the examples or phenomena digress from the mean, they approach the abnormal or the unnatural. This will suggest the merging of the healthy into the diseased state. Assuming further that health is controlled by a harmonious and uniform set of impulses, the interruption of one of them or the introduction of a foreign stimulus will unbalance the cycle, or the natural impulses may be destroyed by the foreign intrusion. Many slight abnormalities of stimulation or minor intrusions are quickly removed and the general physiology rights itself promptly. If, how-

ever, the interruption or intrusion affect an important structure, an organ like the liver or lung, the cycle of physiology of the remaining parts must be constructed upon a new temporary plan in a compensatory manner. The various organs or systems have different values in throwing compensatory work upon others. For example, the failing lung throws work upon the kidneys, skin, and intestines, and the failing heart strains the lungs and kidneys. Organs in pairs complement each other or one may attempt to assume the duties of both. The loss of the liver or kidneys is incompatible with life, while a large part of these organs or even of the brain may be destroyed without cessation of life.

The gross alteration in diseased organs is fundamentally the effect of pathological changes in constituent cells, as Virchow's philosophy has taught us. The severity of an abnormality stands in direct relation to the number of cells affected, the degree of change, and the importance of the cells. The more highly specialized a cell, the less able it is to regenerate its kind, and, therefore, the more lasting is the effect of its destruction. The cells of the brain and the germ cells do not reproduce.

While disease is still viewed as a process which begins anatomically, it is obvious from the above that all diseased states are probably preceded or at least always accompanied by chemical and physiological disturbances. This part of the subject will be taken up in particular in the next chapter. The cause of these anatomical and chemical changes are factors either within or without the body. The specific diseases are usually indicated by an equally specific set of anatomical and chemical changes from the normal.

The *symptoms of disease* are the expressions of abnormal functional activity, and are, therefore, properly discussed under the head of Pathological Physiology; but they are so important from a practical standpoint, and form so extensive a subject of investigation, that they are usually considered apart from pathology, in special treatises dealing with diagnosis and the practice of medicine.

CHAPTER I

THE ETIOLOGY OF DISEASE

THE study of the causation of disease embraces and must account for the predisposing factors and the determining causes. The former prepare the system and make it susceptible to the latter, or immediate and specific causes of disease.

The predisposing factors may increase the receptivity of the body for more than one kind of disease agent. The term "predisposition" is at times used for a hereditary or acquired tendency toward certain diseased states. Thus, one might exemplify hereditary predisposition by the lowered resistance to tuberculosis of the young of tuberculous parents. Another phase of this hereditary influence is shown in the tendency for cells to exhibit an abnormal metabolism because of a family or hereditary tendency, and leading to abnormal states of health (Baumgarten's *anlage*). (See Heredity.) Acquired predisposition is due to vices of living, previous disease, or to a summation of several predisposing factors leading in one direction. This has been termed "disposition" by some writers.

Predisposing Factors.—The normal system is able to cope with the determining causes of disease to a certain point by its general vitality and regulative functions. Thus, heat and cold may prove harmless if not too intense or prolonged. In the case of exposure to heat, the superficial capillaries become dilated, sweating increases, and there is increased heat dissipation from the surface at the same time that increased respiratory function occasions evaporation and loss of heat through the lungs. In the case of exposure to cold, increased muscular exercise leads to greater heat production, while contraction of the superficial blood-vessels restricts the elimination of heat. When, however, a certain point of intensity is reached in the case of heat, cold, or other causes of disease, the normal organism is unable to oppose sufficient resistance, and disease or injury results. Chemical relations in body cells and fluids, such as equilibrium of colloids in solid and liquid condition or enzyme power, may be destroyed by prolonged exposure to heat and cold, and the former may also destroy red blood-cells. The degree of resistance differs in different individuals, in different races, or people living under varying climatic conditions, etc. In some the degree of resistance may be so great that certain diseases are never contracted. The term *immunity* (*q. v.*) is applied to this state.

Certain predisposing factors may now be taken up in order.

1. *Age*.—This plays a large part in the vulnerability of an individual. The exanthemata are much more common in childhood, while carcinoma is commonest in adult life. The rate of repair is also greater in

youth. Tuberculosis assumes somewhat different forms when developing in childhood, adolescence, or adult life. There is a decided variation in the amount of protective antibody in the blood at different ages.

2. *Sex*.—The influence of sex is not great aside from disease of the sexual organs. Man is subject to more traumatisms and diseases due to the wider social life he leads. He suffers more often from cancer, aside from genitalia, than the female. There are more cases of gout, diabetes, and organic nervous disease in men. Women are more often attacked by functional nervous diseases and affections of the thyroid gland.

3. *Race*.—Certain peoples are prone to or immune against certain diseases. Negroes are resistant to malaria and endure yellow fever well. Aside from the unsanitary conditions in which many live, they have a low resistance to tuberculosis. The effect of zoölogical order is more pronounced than race differences. The dog is resistant to tuberculosis; the chicken, to tetanus. This has hampered experimental work upon infectious diseases, because it is often difficult to fulfil Koch's postulates (*q. v.*).

4. *Nutrition*.—Failure to obtain wholesome pure food will, of course, reduce resistance. The presence of putrefaction or disease-producing agents will cause disease. Prolonged hunger reduces general resistance. Habits of any sort that tend to disturb digestion reduce resistance. The maintenance of what is apparently the amount of fat normal to the individual is helpful to resistance. The relation of bodily activity and stored-up reserve has an influence upon later demands of exertion.

5. *Idiosyncrasy* is the peculiar susceptibility of individuals to certain poisons or infections and sometimes even to ordinary foods. This should not be confused with diathesis or predisposition (*q. v.*).

The presence of one infection may favor the reception of another.

6. *Conditions of life*. *Habitation* in places infested with disease-transmitting insects materially influences morbidity. Unsanitary dwellings directly affect health. *Occupation*: Workers in paint suffer from lead-poisoning; handlers of hides contract anthrax; miners get anthracosis of the lungs. Prolonged mental anxiety has some depressing effect upon resistance.

7. *Injury*.

8. *Heat and cold*.

9. *Physical forces*, like electricity and x-ray, and atmospheric pressure.

10. *Poisons* of all kinds.

Items 1 to 5 may be called intrinsic or internal, while 6 to 10 are extrinsic or external.

PATHOLOGICAL DISPOSITION

Under this heading come those instances in which physical or physiological departures from the type or from the standard are expressed in the unusual susceptibility of the whole or a part. Idiosyncrasies might be classed here. This pathological disposition refers chiefly to those conditions in which slow healing of skin wounds or the lack of

sweat and sebaceous secretions render the skin more susceptible to spreading infections. We might also include here the sensitive state of some individuals to certain organic proteins which makes them subject to intoxications with these compounds, not toxic to other persons. (See Immunity.)

There is a related pathological disposition at seats of chronic inflammation, chronic irritation, or chronic injury, as it has lately been called. Here malignant change may occur.

Whether this pathological disposition is hereditary or acquired is difficult to say, as it is equally impossible to decide whether it is due to absence of immunity reactions.

Occasionally organ or system disposition is mentioned, by which is meant a peculiar visceral distribution of lesions, which may be anatomical or physiological. It covers such instances as the frequency of infarction of the spleen and lung, and the involvement of the spleen in liver disease.

Heredity or *inheritance* is a factor of importance in the etiology of disease. In some cases the disease itself is transmitted to the offspring, but more frequently the predisposition only. A distinction must be made between weakness of a child at birth (congenital weakness) and a definitely inherited weakness. Thus, an alcoholic mother or one subjected to hardships during pregnancy may give birth to a child which is feeble and lacking in resistance to disease. This feebleness is congenital, but not inherited. The same statement applies to diseases such as tuberculosis and syphilis, which may be acquired from the mother by the fetus *in utero*, but are not inherited. If the father is the original source of infection, he first infects the mother, from whom the child then acquires the disease. One cannot in these cases properly use the term "hereditary."

Heredity, strictly speaking, applies only to the transmission of parental or ancestral characteristics to the offspring through the parental germ-plasm. We may distinguish between *racial*, *familial*, and *direct* inheritance. The term *direct inheritance* indicates transmission from parent to offspring. The term *indirect* is sometimes used to indicate transmission of characters latent in one generation to subsequent ones. *Atavism* is a more frequent designation of this derivation of characteristics from ancestors after they had been latent in one or more generations. In a broader sense the term "atavism" has also been applied to *reversion* to racial characteristics that had been dormant through many generations. *Collateral inheritance* is a term used in cases in which an individual manifests characters present in uncles, aunts, or other collaterals, but not in his parents or immediate ancestors. The laws of heredity explain this occurrence.

In some cases there is crossed transmission. A peculiar form of heredity is seen in hemophilia and some other diseases, which are transmitted through the female members of a family, who generally remain unaffected, to the male offspring. Hereditary traits sometimes predispose to a number of allied affections. This is particularly striking

in the case of the neuropathic heredity, in which various forms of nervous disease may appear alternately or irregularly in members of an affected family.

Rössle says normal and pathological characters, but not diseases, are inherited. The ovum is not infected with the cause of syphilis, but the fetus is infected with the germ cells or through the placenta. The influence of *maternal* conditions is naturally the greater. Abnormalities in offspring of consanguineous parents are now explained as a summation of the natural tendencies of both parents.

Hereditary Congenital Pathological Conditions.—Such conditions as hemophilia and color-blindness, familial nervous disorders, joint malformations, and skin anomalies are placed in this group.

Pathological Conditions of Later Life Depending Upon Heredity.—This heading refers to the related subjects of predisposition and diathetic reversion or inheritance. Such diseases as gout, diabetes, and insanity are covered. Here one may place the undeveloped physique and constitutional lack of resistance to tuberculosis in the children of affected parents.

A number of theories have been constructed to explain the mechanism of heredity. Darwin, in his hypothesis of pangenesis, suggested that minute particles are given off from all of the cells of the body; these are collected in the reproductive cells, which, in consequence, represent all of the bodily characteristics, hereditary and acquired. Weismann denies the transmissibility of acquired characteristics, and holds that in the process of reproduction a certain amount of "germ-plasm" passes from the parent cell into the offspring, where it remains, and is in turn passed on to succeeding generations, thus perpetuating ancestral characteristics.

Another theory of heredity is called epigenesis, or that process through which an ovum goes in its maturation process when it develops under its appropriate biological environment. This theory does not accept the statement that in the ovum there is a preformed molecule that will eventually develop into a particular part, as is the case with the two previous theories. It assumes that the development of the individual occurs in harmony with that of the race.

However, it has been shown that with the earliest stages of a developing ovum certain differentiations occur which apparently stand as forerunners of certain bodily parts, and the development depends upon the preserved integrity of these primary divisions of the ovum. It has also been shown that an embryo when dividing shows distinct polarity. These facts militated against the epigenetic theory and gave rise to the mosaic theory, which assumes the control of bodily parts by definite molecules or blastula segments.

It must not be forgotten in the study of heredity that, while the atomical changes are measures of evolution and heredity, the chemistry of the biological mass must be similarly affected. If, as has been maintained by some authors, the disproportion between the surface tension in nucleus and protoplasm combined with alterations in the

chemical constituents as a result of this, be the cause of cell growth, then any disturbance of the cell tension or chemistry will be felt by new cells the product of the division. If the parent cell has established for itself a definite chemical cycle its progeny will continue this cycle. This is another application of Baumgarten's anlage, and shows the close association of heredity and predisposition.

The theories and experiments upon heredity have given rise to certain generalizations and laws which are now explained.

Racial inheritance expresses itself in functional or anatomical variation. Races are peculiar in resistance to parasitic diseases and in the maintenance of certain physical characters.

Familial inheritance is similar in principle to the former, and is well illustrated in hemophilia (*q. v.*).

Blended and Particulate Inheritance.—The former means a harmonious admixture of characters of the parent, while the latter means the domination of some particular character. *Mendel's law*: The observations of Gregor Mendel upon self-fertilizing plants showed the transmission of character to follow a very definite law. When two organisms, one so-called dominant, the other recessive, reproduce, the offspring contains a mixture of the two, although dominant characters may show more clearly. The second generation shows one pure dominant, two admixtures of dominant and recessive, and one recessive. Self-fertilization will produce always dominant from dominant and recessive from recessive. Offspring of admixtures will produce, as in the second generation, a dominant which will continue a dominant, a recessive following this type in its progeny, and mixtures of dominant and recessive and recessive and dominant. These last two will then follow the same course by producing two pure and two mixed progenies. This law has been worked out with many plants and some small animals. It has not been directly applied to man, but it is obvious that the domination of characters must have influence upon offspring. Galton's law claims that the parents each supply a quarter of the influence to the offspring; the four grandparents, each a sixteenth, and so backward to the completion of the unit.

For the *mosaic inheritance* and *atavism* see above.

Reversionary inheritance is atavistic reversion to a lower condition or incomplete type.

Diathetic inheritance is a transmitted tendency in a particular direction. (See Pathological Disposition and Predisposition.)

Cumulative inheritance is a summation or exaggeration of characters from both parents.

Mutation is the assumption of character not peculiar to the given species.

Determining Causes.—Among the immediate or determining causes of disease are those which originate outside the body and those which are generated within the body. Among the former are included traumatism, heat, cold, and other physical agents, poisons, and living organisms, including bacteria and various animal parasites. The causes of

disease originating within the body itself are less definitely known, but it has been found in chemical studies that various products of normal metabolism when accumulated in abnormal quantity, or products of disturbed metabolism, may occasion local or widespread disease of various sorts. This self-poisoning is designated auto-intoxication.

The term "auto-intoxication" is frequently applied to poisoning by products of intestinal putrefaction. This application of the term is not, strictly speaking, correct. The same poisons might have been produced by putrefaction of food outside the body, when the use of the name auto-intoxication would be manifestly absurd. If poisons are produced by imperfect digestion, and these affect the organism, the condition could properly be termed auto-intoxication.

TRAUMATISM

Traumatism, or mechanical injury, may be of various sorts, gradual or sudden, small or large; and the effects are dependent upon the form and severity of the injury. *Pressure* brought to bear upon a part leads to disturbances of the circulation and more or less direct injury of the cellular elements. When the pressure is gradual, true atrophy of the part may occur, as in the case of the atrophic liver resulting from lacing. When the pressure is greater and the circulation is completely arrested, more destructive change may result, such as necrosis or gangrene. This is seen in the necrotic atrophy of bone resulting from the pressure of aneurysms, or the gangrene of extremities resulting from ligation. *Wounds*.—Frequently, inflammatory reaction occurs in the surrounding tissues when traumatic injuries have been sustained. This is illustrated in all forms of wounds, and it is through the inflammation and subsequent regeneration of tissue that the areas of destruction are restored. In cases of injury by fine particles, as in powder-marks of the skin, or the surface injuries sustained by miners and metal-workers, or in individuals inhaling sharp particles like coal-dust, marble-dust, or steel-filings, small injuries of the tissues result. The foreign bodies may be subsequently discharged, leaving a focus of inflammation, or the inflammation may surround the particle embedded in the tissue, and encapsulation by fibrous-tissue formation may occur. Large injuries in which the tissues are contused or broken may lead to extensive inflammation, in part the result of the direct injury to the tissues and in part the result of injury of the blood-vessels.

An injured surface presents a *locus minoris resistentiæ* which offers an entrance to organisms already in the locality or to those that might be actually driven into the tissue or blood-stream by the damaging force.

Gross traumatism of the body as a whole, as in falls, crushing injuries, etc., causes various disturbances according to the part mainly involved. Rupture of the viscera, as the lungs, heart, liver, spleen, stomach, or intestines, may occur. When the head is violently struck, unconsciousness is common as a consequence of either disseminated punctiform hemorrhages, large focal hemorrhages, or obscure and

possibly only functional disturbances. *Commotio cerebri*, the condition occurring in such cases, may be fugacious or may lead to permanent disorder dependent upon organic changes in the brain. Spinal symptoms, met with after railway injuries and like accidents, may be due to hemorrhage and secondary morbid processes in the cord, or may be due to the uncertain pathological conditions constituting hysteria.

The relation of a single trauma to tumors is not entirely clear. It seems that a new growth has been observed at a point where an injury has been sustained. Repeated minor traumata or continued irritation seem to precede some epithelial growths. The most notable example is the epithelioma of the lip of clay-pipe smokers. The injury in these cases can hardly be a determining cause. The occurrence of a tumor at a site of injury is not inconsistent with any of the principal theories of cancer origin.

Epithelial cysts may arise at points of injury by the displacement of epithelial cells to a position below the surface. These are not true neoplasms.

PHYSICAL CONDITIONS

Heat.—High temperatures produce local or general results according to the mode of application and degree of heat.

Local excess of heat produces various lesions. Moderate excess leads to relaxation of the walls of the blood-vessels; with increasing grades of temperature there is, in addition, necrotic change in the cells of the part, and exudation of serum causes vesicle formation. Still higher grades of temperature produce immediate destruction, perhaps with charring, of large or small areas, while the surrounding tissues suffer from reactive inflammation and hyperemia. Extensive burns involving one-third or more of the surface of the body frequently cause death. In these cases it is likely that poisonous products are formed, either directly through tissue and blood destruction, or indirectly through disturbances of the functions of the skin or internal organs. The immediate manner of death is often in the form of shock; when the termination is delayed, various vascular, hemic, and tissue disturbances may occur. Intravascular coagulation is not unusual, and is not improbably the result of the liberation into the blood of tissue elements set free in the areas of local destruction, or to substances produced by direct destruction of the blood. The same substances may account for the existence of fever (ferment intoxication). The intravascular coagulation caused in this or other ways may induce venous stasis and localized hemorrhages. Focal necrosis or degeneration of the tissues of various organs, such as the liver, kidneys, or the mucous and serous membranes, may be due to thrombotic occlusion of vessels, or to the influence of circulating poisons without thrombosis, or to both. It seems probable that the cause of all these physical changes is a necrotizing toxin arising in the burned skin. (Some manifestations of this condition resemble anaphylaxis.) Marked changes are found in the lymphatic glands as well as in the Malpighian bodies of the spleen and in the bone-marrow. These changes present themselves as areas of leukocytic degeneration

containing actively phagocytic endothelial cells and surrounded by a zone of lymphocytic invasion. The lesions are not unlike those produced by abrin, ricin, and bacterial toxins. Duodenal ulcer is often referred to as an occasional result of extensive burns. The blood itself may present evidence of disease in the form of degenerations of the corpuscles, in the reduction of their number, and of the amount of coloring-matter; while regenerative changes frequently present themselves some time later (nucleated red corpuscles). Changes in the urine may occur in cases of extensive burns, in consequence of the tissue destruction (hemoglobinuria, albumosuria).

Exposure to general high temperature varies in its effects according to the manner of exposure (dry air, steam, etc.). An animal exposed to a constant temperature somewhat above the usual surrounding temperature presents a slight increase of its body heat, which is compensated for by increase in the respirations and pulse-rate. Much higher temperatures may cause death by coagulation of the tissue proteins, notably in the muscular structure of the heart or the respiratory muscles. Before this extreme is reached, however, it may be found that the consumption of the tissues of the body is greatly in excess, though the respiratory quotient is altered in favor of the amount of oxygen consumed. Continuous exposure to excessive heat frequently causes peculiar disturbances in man, known as heat-stroke, sunstroke or insolation and heat exhaustion. In these conditions hyperemia and edema, or even inflammation of the meninges, may occur. These lesions are sometimes supposed to be the result of the direct effect of the heat; but there is reason to believe that they may be occasioned by poisonous substances produced within the body by disturbed metabolism, as a result of the heat. One evidence of the effect on the blood of continued elevation of temperature is the appearance in the red blood-corpuscles of basophilic granules—granular degeneration of Grawitz. (See chapter on Blood.) Exposure to high temperatures for long periods, such as steamship stokers are subjected to, produces cramps in the muscles, chiefly of the extremities. The excitability of the muscles is greatly increased.

The autopsy upon a death from heat-stroke shows an early rigor mortis and decomposition, general passive congestion due to weak heart action, a fluid condition of the blood, and sometimes hemorrhages into the medulla.

A portion of the body, as an arm or a leg, may be exposed for a limited time to excessive temperatures (300° to 400° F.) in dry air without injury. The general temperature is slightly elevated, but metabolism is practically unaffected.

The effects of general or local heat are much increased when the organism as a whole or in the part involved is below par. A paralyzed limb is burned or scalded at comparatively low temperatures.

Cold.—Exposure to extreme degrees of cold may cause results quite similar to those produced by heat. Exposure of the skin to liquefied air, solidified mercury, or other substances at excessively low

temperatures produces vesiculation and necrosis of the tissues like those produced in burns.

Exposure of the body to greatly reduced but bearable temperatures of the surrounding atmosphere causes vascular disturbances followed by necrosis of the tissues and inflammatory changes. The parts so affected are the extremities or projections of the body, like the toes and fingers, nose and ears. The primary result of cold is vascular constriction and local anemia. These serve the purpose of preserving the body heat by preventing heat radiation; later the blood-vessels are paralyzed and extreme hyperemia results. Then cellular exudation and necrosis may occur. These changes are well seen in the condition termed *chilblain*. In prolonged exposure to cold there are a gradual reduction in the activity of the various organs and a gradual obtunding of the sensibility until the patient becomes comatose. The retention of excrementitious products of metabolism, or the formation of products of abnormal metabolism, may be important in causing this condition. There is a reduction of hemoglobin and red cells, increase of CO₂ excretion, and disappearance of glycogen. Autopsy shows edema of lungs, with or without congestion, and transudates into serous cavities.

Exposure to cold plays an important part as a clinical cause of disease. Various forms of pharyngitis and coryza or bronchitis so frequently follow such exposure that the term "cold" is generally used. Other conditions, like rheumatism, pleurisy, pneumonia, and the like, bear a similar relation. It is now recognized that in most of these cases cold is merely a predisposing cause, the immediate cause being in many, if not all, cases specific micro-organisms. The mode of action of the exposure is uncertain; probably it causes a reduction in the resisting powers of the organism and thus favors the activity of bacteria. The hyperemia following exposure to cold is associated with lowered alkalinity of the blood, thus favoring bacterial increase. The phagocytic action of leukocytes is reduced by exposure to cold, and it is said that complement and antibody do not combine so readily with antigen. This is true *in vitro*.

Increased Atmospheric Pressure.—Exposure to extreme pressure of several atmospheres may occur among deep-sea divers or in men working in caissons used in bridge building. But little disturbance may be caused at first or for a long time; but on return of the workmen to the usual atmospheric conditions symptoms make their appearance (caisson disease). Among these symptoms are bleeding from the nasal or other mucous membranes, great depression, delirium, and paralytic conditions. Congestion, degenerations, and vacuolations in the spinal cord have been discovered in some cases.

The cause of the lesions is a hypertension of nitrogen within tissues. Tissues hold much more nitrogen than the blood, so that this gas is held in them because the blood becomes saturated each time it passes through the lungs. When the person returns to normal atmospheric pressure the tissues give up to the blood their retained gas. The blood and lungs can excrete but slowly, so that bubbles of nitrogen under release

of pressure appear in tissues and vessels. These bubbles are the cause of hemorrhages, fissures, and gas embolism.

Decreased Atmospheric Pressure.—Effects of decreased pressure are seen in inhabitants of high altitudes and in persons ascending in balloons. Marked excitement of the vascular system, hemorrhages, somnolence, weakness, vomiting, and similar symptoms are observed; in less marked cases a general excitement of the nervous system, sleeplessness, etc., occur. These symptoms have been attributed to lack of oxygen, and compressed air and oxygen have been successfully used to combat them; but experiments show that the air-pressure may be as low as 400 mm. of mercury without interference with the respiratory exchange of gases. To a certain extent the symptoms are probably mechanical and due directly to the reduced pressure on the exterior. Recent studies show that the blood contains greatly increased numbers of red corpuscles in a given volume, and the percentage of hemoglobin is correspondingly increased. This is probably due, to some extent, to disturbance in the distribution of the corpuscles with stagnation in the peripheral vessels (see Diseases of the Blood).

Insufficiency of Respiratory Air.—A certain amount of air is necessary for the continuance of health or life. Insufficiency may be due to diseases which obstruct the air-passages or affect the pulmonary tissue itself, and to foreign bodies (solid bodies, water in drowning) within the air-passages. Changes in the atmosphere or gases taken into the lung may cause insufficiency in the supply of oxygen, notably in CO-poisoning, in which the foreign gas enters into firm combination with the hemoglobin of the blood and thus excludes oxygen.

The respiratory rhythm is maintained by the appropriate stimulation of the respiratory center by the appropriate mixture of carbon dioxide and oxygen in the circulating fluids. If, by repeated deep inspiration, the amount of CO₂ in the blood decreases (called *apnoea*), there is no stimulation of the respiratory center and a condition of true apnea ensues. This view of apnea is maintained by some, while others claim that apnea may be induced after section of the vagus, and that, therefore, the gases in the blood are always responsible for apnea. This term should be used for the interruption of respiration due to the above causes, and not to cessation by mechanical or voluntary causes.

Moderate decrease of the supply of air causes labored and rapid breathing, more or less cyanosis, depression, and stupor. This condition is termed *asphyxia*. Complete lack of air causes increase of these symptoms and death by *suffocation*. In these cases the blood is exceedingly dark and fluid, and hemorrhages may be found in various situations. The latter result from excessive blood-pressure during the death agony. Long-continued insufficiency of oxygen may directly or indirectly occasion degenerative diseases of the tissues.¹

¹ It has often been asserted that anemia causes many of its symptoms and results because the blood is incapable of carrying sufficient oxygen in its reduced state. As a matter of fact, however, physiological experiments have demonstrated that the respiratory exchange (inhalation of oxygen and exhalation of carbonic acid gas) is but little affected and is as frequently increased as decreased.

Electrical Influences.—The effects of powerful electrical currents and discharges on the tissues resemble those produced by burns. Locally, a dry, crisp, excavated lesion is produced. Later, hyperemia and appearances resembling moist gangrene develop. The underlying muscles are more or less parietic. Changes in the blood-vessels and a fluid state of the blood, extending to some distance from the local lesion, have been observed. Very powerful and fatal discharges in some cases produce hemorrhages in the floor of the fourth ventricle and petechiæ in the serous membranes and elsewhere. There are degenerations of nerve-cells, particularly in ganglia. Death seems to be caused by powerful inhibition of the heart. Lightning stroke leaves branching linear burns. Less powerful discharges, such as dynamo workers receive, cause stinging sensations in the absence of burns. If prolonged, there is loss of consciousness, depending for its depth upon the amount of and duration of the current. There is no definite amount that the body will always endure.

Effects of X-rays.—Exposure of healthy or unhealthy tissues to x-rays causes cellular degenerations and necroses with secondary inflammatory reaction. The skin—being most immediately exposed—is the most susceptible of normal tissues; but diseased tissues and new growths are still more readily affected, probably because of their less stable condition. The point of severest attack is the nucleus of young specialized cells. The epithelial cells of the skin suffer first and most intensely; the glandular cells of the skin are less prone to degeneration. The damage to the skin by x-ray is followed by a chronic dermatitis like xeroderma pigmentosum. This shows a tendency to go over into epithelioma. The x-ray affects the hematopoietic organs by destroying the essential early leukocytes (karyorrhexis in the germ centers in lymph-tissue and reduction of the myelocyte series in bone-marrow). There is some basophilic degeneration and polychromatophilia of the erythrocytes. X-rays may affect the genital organs by destroying the spermatozoa without producing physical impotence; by causing menstrual disturbances and abortion. After prolonged raying sexual gland atrophy may ensue. X-ray affects metabolism by increasing uric acid nitrogen and phosphorus excretion and by splitting body lecithin. Swelling and degeneration of the endothelial and other cells of the blood-vessels and thromboses may in part account for some of the results of x-ray exposure.

POISONS

Definition.—The term “poison” may be applied to substances which when introduced in relatively small amounts into the living organism disturb its structure or functional activity.

The Action of Poisons in General.—Gaseous poisons act primarily upon the respiratory mucous membranes with which they come in contact, or after absorption into the blood disorganize this fluid or lead to disturbances of the nervous system. Liquid poisons are generally absorbed through the gastro-intestinal mucous membrane, but may be

received directly into the tissues by injection under the skin. They are rarely absorbed through the skin. Solid poisons must in all cases first be dissolved, and are then absorbed like the liquid poisons. They may by their strong attraction for water absorb the latter directly from the tissues, and by this process alone may bring about important changes.

The lesions due to a poison may be entirely local, as in the case of certain corrosives or caustics; in other cases the point of entrance is unaffected, the pathological manifestations being entirely due to the changes in different parts of the body, or to nervous disturbances resulting from the circulation of the poison in the blood. Some poisons act immediately in destroying cells (caustics), while others must combine with them before the toxic effect is manifest; in other words, there is a latent period.

The **fate of poisons** after ingestion is very different in different cases. Some poisons circulate with the blood and are eliminated unchanged. Others may suffer chemical change within the stomach or other cavities of the body before absorption, and may be either completely neutralized, or may be converted into forms which are subsequently slowly absorbed. After absorption into the blood other chemical reactions may occur, and the poison may be more or less neutralized, the system then suffering either from the resulting compounds or from the changed condition of the blood. Active destruction of the poison may occur in the blood or in the various organs, especially the liver. In these processes, however, the glandular organs may suffer seriously, various forms of degeneration or necrosis resulting. Certain poisons, like the toxins, enter into chemical combination with cells of the body and remain fixed in this way. (For further details see Immunity.)

The defense of the body against poisons lies in substances natural to it, and probably not increased in response to intoxication. This does not apply to the bacterial toxins in bacterial infection, but if injected in the absence of general infection some of the bacterial toxins may be detoxicated as are inorganic or higher vegetable poisons. Among the defensive bodies are the blood, bile salts and acids, sulphuric acid as such or as sulphates, and the fatty acids. The processes at work are rapid elimination, oxidation, reduction, and hydrolysis. Poisons may be changed in form by precipitation or altered by combination with body proteins.

The **effect of poisons** depends upon the dose as well as upon the nature of the substance, and also upon the individual. The repeated ingestion of certain poisons, such as arsenic or opium, may generate a considerable degree of immunity or tolerance (mithridatization). Similar immunity may be a natural characteristic of a given individual or of classes or species. Susceptibility to the action of poisons is further influenced by age and constitutional vigor. Children bear certain poisons better, comparatively speaking, than adults, while the reverse is true of other substances. Sometimes there are idiosyncrasies which

lead to peculiar results not observed in the average individual. In consequence of this, substances ordinarily not toxic may be extremely injurious to certain persons. (See Allergie.)

Sometimes poisons are comparatively innocuous when administered in one way, though powerfully toxic to the same animal when otherwise introduced. Thus in dogs intravenous injection of atropin is very slightly injurious, but injection of minute doses into the spinal cord causes rapid poisoning. Some experiments would indicate that the leukocytes are capable of fixing inorganic poisons and thus acting as defensive agencies. Non-fatal doses of poisons (arsenic) cause, first, diminution of the polymorphonuclear leukocytes, followed by leukocytosis; and the poison is found in abundance in these leukocytes. Fatal doses are unattended with the secondary stage of leukocytosis or the leukocytic fixation of the poison. These results need further confirmation.

In general, the action of poisons may be immediate destruction, stimulation to exhaustion and disintegration, or inhibition gradually to cessation of function. There are poisons with special predilection, *e. g.*, strychnin for the nervous system; phosphorus for bone; snake-venom for blood, nervous tissue, and spleen.

Elimination.—The excretion of poisons may take place through the kidneys, lungs, the mucous membrane of the gastro-intestinal tract, the mammary glands, or the skin. In some instances a poison is eliminated without change in the excreta; in other cases it suffers complete change, and is not present at all in the excretions. The rate of elimination varies greatly, and is more or less dependent upon conditions of the system. Some poisons, as phosphorus and mercury, may be stored up within the body for a considerable period, subsequently suffering slow elimination.

Classification.—The number of substances which may act as poisons is very great, and the manifestations are of very different sorts. Classification of poisons is, therefore, difficult and not entirely satisfactory. We may crudely distinguish between gaseous, liquid, and solid poisons; between animal and vegetable; organic and inorganic; but these classifications have no scientific value.

From the point of view of the action of the poisons we may distinguish *corrosive poisons*, or those which have a local action; *organic* or *parenchyma poisons*, or those which act less strongly at the point of application than upon the various organs to which they are conveyed through the blood; *blood-poisons*, or those which exercise their effects primarily upon the blood; and the *nerve-poisons*, or those which disturb the functional activity of the nervous system without producing definitely discoverable lesions.

Corrosive Poisons; Escharotics; Caustics.—Under this heading are included various acids, alkalies, and mineral poisons, such as sulphuric, nitric, oxalic, carbolic, and hydrofluoric acids, caustic potash or soda and ammonium, and gases like chlorin and bromin. Nitrate of silver, bichlorid of mercury, sulphate of copper, and other inorganic

compounds have a similar action, and certain organic bodies, such as cantharidin and croton oil, belong to the same class.

All these poisons exercise a destructive effect upon the cells with which they come in contact, partly by abstraction of water and partly as a result of a coagulating power or similar action. The acids and mineral caustics usually produce dry and more or less discolored areas of necrosis; the caustic alkalies cause a sort of gelatinous change or a saponification of the tissue. The degree of injury depends upon the poison and the amount in contact with the tissues. There may be only a superficial injury of the outer layer of epithelial cells, or extensive destruction. Reactive inflammation is almost always present, and often, especially in the mucous membranes, the inflammatory reaction is extensive, though the corrosive action of the poison is limited in depth and extent. The affected part may present slight areas of necrosis with reactive hyperemia and inflammation beneath and around them, or deep eschars, vesicles, or large bullæ. In the process of healing, extensive scars may form, and these may be serious in their effects, as in the case of strictures of the esophagus.

Organic Poisons; Parenchyma Poisons.—This large group includes many metallic compounds that have a local corrosive or escharotic effect, but which may in smaller dose gain entrance to the blood and cause extensive organic lesions. It also includes poisons of vegetable origin and products of bacterial growth. In general, these poisons have a similar action. The kidneys and the mucous membrane of the intestines are especially active in their elimination and suffer most seriously. Degenerations of the epithelial cells of various sorts are met with, such as nuclear degenerations, coagulation necrosis, fatty degeneration, and even calcification. The changes may be diffuse or may occur in small foci. In the latter case small areas of granular appearance, having a lighter color than the surrounding tissues, are seen; and on staining the cells are found to color poorly or not at all, the nuclei often showing this change first. Nuclear degenerations (fragmentation, hyperchromatosis, etc.) are observed, and in some instances marked fatty degeneration of the cells occurs. Around the foci of degeneration there is more or less cellular infiltration (polymorphonuclear cells), and to a less degree the degenerated area itself is infiltrated. In cases in which diffuse change occurs there is equally diffuse round-cell infiltration. After the acute process has subsided, hyperplasia of the connective tissues may occur and the affected part becomes more or less sclerotic or indurated. Regeneration of the parenchyma cells is less apt to occur.

Some of the more important of the poisons of the group may now be separately considered.

Phosphorus is a poison of considerable activity in the yellow form; the red variety is inert. Workmen in match factories are the most frequent victims of this form of intoxication, but occasionally accidental poisoning by swallowing occurs. In the latter the manifestations are acute. The pathological changes are catarrhal inflammation of the

gastro-intestinal mucous membrane and more or less widespread fatty degeneration of various tissues and organs. The liver suffers most severely, being enlarged, light yellow or reddish in color, and friable or doughy. Microscopically, the liver-cells are found extensively degenerated (fatty). Similar but less marked fatty degeneration is found in the renal tubules, gastro-intestinal epithelia and heart-muscle, and in the intima of the blood-vessels. Extensive jaundice is frequent and numerous hemorrhages may occur. In the more chronic poisoning of match-makers the poison enters through the mouth and respiratory passages, being inspired as dust. Chronic catarrhal inflammation of the respiratory tract may occur and a peculiar form of necrosis of the bones (see Bones) is met with.

Arsenic is poisonous in certain forms (white arsenic, arsenous acid) and inert in other forms (the sulphids). Acute poisoning occurs when toxic forms are swallowed in large doses; the chronic forms of poisoning result from gradual ingestion or the inhalation of dust containing arsenic. Cases of the latter sort occur when wall-paper, hangings, and the like, colored with arsenic pigments, are used. The lesions in acute arsenic-poisoning resemble those produced by phosphorus. The gastro-intestinal inflammation is, however, more severe; while the fatty degeneration of the organs is less marked. In chronic arsenic-poisoning changes in the peripheral nerves (degeneration and inflammation) are most important. It is likely that focal or diffuse myelitis may likewise be caused by this poison. Chronic inflammations of the gastro-intestinal or respiratory mucous membranes are met with in some cases. Inflammatory lesions and pigmentation of the skin may occur.

Lead.—Among the compounds leading to acute or subacute poisoning the chromate, the acetates, the carbonate, and oxid are most important. Chronic poisoning occurs in workmen in paint manufactories and among type-setters and painters, and in persons drinking certain waters that have been conducted through lead pipes. Less rarely the use of cosmetics, dyestuffs, etc., containing lead causes chronic poisoning. In the acute forms of lead-poisoning moderate gastro-enteritis occurs. In the chronic form changes in the nervous system are most important. Peripheral neuritis is the most frequent lesion, but changes in the large ganglionic cells of the gray matter of the cord have sometimes been found. Diffuse sclerosis of the blood-vessels, interstitial nephritis, and the lesions of gout may be present. Atrophy and fatty degeneration of the muscle-fibers are less important results. A blue line on the gums at the junction with the teeth (due to deposit of sulphid of lead) is a lesion of clinical importance. A constant and diagnostically suggestive change is found in a peculiar degeneration (basic degeneration) of the erythrocytes. (See chapter on Blood.)

Mercury.—Poisoning with mercury may be acute, subacute, or chronic. The first is due especially to the corrosive chlorid and other mercuric salts; the second, to calomel or small doses of those of the former group. Chronic poisoning occurs as a result of inhalation of

fumes or dust containing mercury, and is seen in workmen in mirror manufactories. In the acute cases violent inflammatory and necrotic lesions of the gastro-intestinal tract are seen. Parenchymatous degeneration, fatty change, and even calcification of the renal epithelium may occur; and fatty degeneration in other organs may sometimes be met with. In subacute cases marked by ptyalism some change is doubtless present in the salivary glands, but the nature of this has not been determined.

Ergot is a poison capable of producing intense toxic results. It contains two important toxic principles, sphacelinic acid and an alkaloid, cornutin. Acute poisoning sometimes results from overdosage; while chronic intoxication occurs from the use of affected grain, particularly in famine years. Widespread poisoning of communities has sometimes resulted. The lesions produced are not definite or uniform. Gastro-intestinal inflammation and erosion of the mucous membrane have been observed, but are not constant; sclerotic change in the spinal cord has been found in a few cases. Gangrene is a frequent lesion, probably resulting from vascular obstruction due to contraction of the blood-vessels. Enlargement of the spleen has sometimes been noted.

Toxalbumins from Plants.—Certain vegetable bodies, like *ricin*, derived from the castor bean, and *abrin*, derived from jequirity bean, are exceedingly toxic, acting in part as blood-poisons, but also as parenchyma poisons. Injected into animals these substances cause violent intoxication and focal areas of necrosis in various situations, notably in the liver. In part these lesions result from vascular thrombosis; in part, from direct action. The study of the action of these poisons is of particular interest from the resemblance of the lesions to those caused by certain bacteria and bacterial poisons.

Toxic Products of Bacteria.—In the growth and multiplication of various bacteria definite toxic substances are created, and through the latter the lesions of infection are to a large extent produced. Such poisonous bodies may be generated in the growth of the bacteria outside of the body, as well as within the body. In the latter case the pathological lesions at the point of infection may be the focus of origin of toxic substances which are then distributed throughout the body. This is eminently true of tetanus and, to a large degree, of diphtheria. In other cases the bacteria themselves are transported to various parts of the body and, finding lodgment in the tissues, set up changes by which their toxic products are evolved. The latter increase the local foci of pathological change and then spread in the circulation and cause general intoxication. Further reference to these poisons will be made when discussing the individual bacteria.

The **venom of serpents** and of **various insects** contains toxic bodies, some of which are albuminous in nature. These vary in their action, being to some extent blood-poisons, but more particularly parenchyma poisons. The lesions produced are local and general. Locally, there are intense inflammatory reaction and edema around an area of cellular

necrosis or destruction where the poison has come in immediate contact with the tissues. The blood seems to suffer great disorganization and corpuscular change. Petechial hemorrhage and foci of cellular necrosis occur in various organs, and edema of the lungs is frequently present. The action of the venom of different animals varies in kind and intensity to a certain extent, but is, in general, of a similar type. Snake-venom has the peculiarity of setting up immunity reactions similar to those induced by bacterial toxins. It contains several different fractions, those toxic to blood, nervous tissue, kidney, etc.

Blood-poisons.—Various liquid or gaseous substances are termed “blood-poisons” because of their especial action upon this tissue. The blood-poisons may be classified as (a) those which combine with the hemoglobin without changing the corpuscles; (b) those which alter the red corpuscles and the coloring-matter; (c) those which affect the blood as well as the tissues generally; (d) those which cause changes in the blood-plasma, increasing or decreasing the tendency to clotting; and (e) those which destroy leukocytes.

(a) Among the poisons which act by entering into combination with the hemoglobin without changing the corpuscles, carbon monoxid, cyanogen, and hydrogen sulphid are important. In carbon-monoxid poisoning, which often results from inhalation of the fumes of charcoal burning with insufficient air, the blood has a light color and light petechial discolorations may be seen in various parts of the body. In cyanogen-poisoning the blood is similarly light in color; while in H_2S -poisoning the blood is often dark, sometimes quite black.

(b) Among the poisons which disorganize the blood-corpuscles and later the hemoglobin are a large number of chemical agents used in medical practice or in the arts, including potassium chlorate, nitroglycerin, anilin, nitrobenzol, various coal-tar derivatives, and arseniuretted hydrogen. Certain poisonous plants (toadstools) act similarly. These poisons lead to a reduction of the hemoglobin with formation of methemoglobin and at the same time destruction of the corpuscles themselves, with release of the hemoglobin into the serum. The altered condition of the blood often induces secondary changes, such as fatty degeneration and hemorrhages in various organs. The blood-corpuscles are found in variously degenerated conditions, showing microcytosis and poikilocytosis in particular. Nucleated red corpuscles may be present as in other conditions of blood destruction with attempted regeneration.

(c) Among the poisons which disorganize the blood and at the same time cause changes in the parenchyma of organs, reference has been made to abrin and ricin. In addition to the organic changes, these substances cause certain alterations in the blood itself, increasing the coagulability and thus inducing thrombosis.

(d) Various substances introduced in sufficient quantity are capable of affecting the plasma of the blood or the corpuscles in such a way as to affect its coagulability. Calcium salts, carbonic acid gas, and fibrin ferment are active in this way, but the last alone produces toxic results

through this function. Ferment intoxication may occur in consequence of various other intoxications, when corpuscular or tissue destruction has liberated the ferment. Among the poisons which decrease coagulability peptone (albumose) is important.

(e) Saponin and benzol destroy leukocytes.

Injection of large quantities of water or hypotonic salt solution may have a hemolytic effect.

The blood-serum of one individual may contain hemolytic agents for the cells of another person, and more frequently for those of another species

Nerve-poisons.—This group contains a large number of substances capable of producing violent symptoms and even death without definite change in the tissues of the body. Certain investigations showing certain alterations in the finer structure of the nervous system in disease and in cases of intoxication suggest that histological changes in the central neurons may be found to result from poisoning by these substances. Changes of this kind (changes in size and form of the cell and nucleus, thickening, contraction, or disappearance of dendrites, alterations in the chromophilic bodies, etc.) have been described in the gray matter of animals poisoned with alcohol and certain toxins of bacterial origin. It is not unlikely that similar changes will be found in other conditions. Among the nerve-poisons are alcohol, chloroform, ether, and various alkaloids like morphin, atropin, etc. In this same group might be included some of the poisons contained in the venom of serpents and other animals, but these usually cause definite lesions in the blood or tissues of the body.

***ptomain* Intoxications.**—Another group of poisons with action similar to the last are those produced within the body by putrefactive action or in various foodstuffs before ingestion. Frequently cases have been observed in which all the members of a family or even large numbers of people have been poisoned by eating certain meats, sausages, ice-cream, and other foods. In some of these cases it has been found that the toxic element was a basic compound resembling the alkaloids in chemical structure. To these putrefactive compounds the name *ptomain* is given. One of these compounds, which occurs in cheese, and occasionally in milk, has been termed "tyrotoxicon." Intoxications of this class must be distinguished from infections resulting from the use of food contaminated with micro-organisms. The symptoms may be so rapidly developed (absence of incubation period) and so immediately generalized that the distinction can be arrived at clinically, but the absolute diagnosis is made bacteriologically. (See p. 37.)

These conditions in food are usually set up by anaërobic bacteria. The pathological results are paresis of the centers of special sense, degeneration of ganglion cells, and hyperemia of all organs. The intoxications usually arise from the intestinal tract and are due to changes in meat by bacteria present in the slaughtered animal before death. The poison is thermostable and does not affect the appearance or odor of meat and may not change the flavor. The symptoms are vomiting,

colic, and diarrhea, followed by collapse. The active agents are bacterial products in the meat, but which can also be obtained by growth of the same organisms *in vitro*. It is an intoxication and not a bacterial infection. *Bacillus enteritidis* of Gärtner is the most important single organism in this group.

A considerable number of ptomains have been separated, including neurin, obtained from putrid flesh; muscarin and ethylendiamin, derived from decayed fish; mydalein, and mydatoxin. Some of these substances produce toxic results indistinguishable clinically from those produced by certain alkaloids. This fact has become one of great importance in medicolegal investigations.

VEGETABLE AND ANIMAL PARASITES

Vegetable parasites are by far the most important causes of disease. The belief in a living cause or *contagium vivum* is by no means a recent acquisition, but the actual demonstration that diseases may be caused by minute living organisms has only recently been reached. The micro-organisms in question (bacteria) belong for the most part to the vegetable kingdom and constitute the lowest orders of fungi. Their biological characters and their relations to special diseases will be described in a subsequent chapter.

Etiological Relationship of Bacteria to Disease.—It is difficult to prove the specific relation of bacteria to disease. Koch has laid down four important laws which must be conformed with before the etiological rôle of a bacterium is admitted. These are: (1) The bacterium must be found in the diseased person; (2) it must be cultivable upon media outside the body; (3) pure cultures introduced into a healthy animal must produce the disease in the animal; and (4) the bacterium must be recoverable from the body of the animal. In a number of diseases micro-organisms have been proved to be the specific causes according to the requirements of Koch's rules. In other diseases it has not been possible to furnish absolute proof, though the presumptive evidence, furnished by constant occurrence of the bacteria, suggestive association with the lesions of the disease, absence of the bacteria in other diseases, etc., is sufficient to satisfy all but the most skeptical.

Classification of Diseases Due to Bacteria.—The general term *infectious disease* is applied to all such as are caused by bacteria. In some cases the diseases are readily communicated from person to person, even though contact has not been immediate. These are termed *contagious diseases*, while the term *non-contagious* is given to those in which such ready transference is not observed. As a matter of fact, the distinction is artificial. Any infectious disease may be communicated from the diseased to the healthy if the germs or bacteria are transferred. In some diseases this transference readily occurs, even through the air and at considerable distances; in others actual contact is necessary; while in still others secretions or excretions of the diseased must be conveyed to the healthy. Contagiousness is, therefore, a matter of degree

only. It is better to use the terms *communicable* or *transmissible diseases* for those in which every case is dependent upon a preëxisting one, the mode of transmission being either direct or indirect. Malaria is an indirectly transmissible disease requiring the intervention of the mosquito, while diphtheria is a directly communicable infection, no agent being required for its spread.

Infectious diseases may at times spread in communities, affecting large numbers of people. Such a dissemination is termed *epidemic*, and the disease an *epidemic disease*. When the disease spreads over large areas, as a whole country or continent, the term *pandemic disease* is applied. Other infections are constantly present in a locality; for such the terms *endemic* and *endemic disease* are used. Some endemic diseases are restricted to certain localities and seem in some measure dependent upon local conditions (of atmosphere, soil, etc.) for their continuance. These are called *miasmatic diseases*. The soil, etc., have, of course, nothing directly to do with disease, but merely afford the conditions necessary for the propagation of the infecting agent, as, for example, swamps and the malarial mosquito.

Infectious diseases are frequently described as *local* or *general*. Local infections are those that present specific pathological change in a restricted part of the body; the general organism suffers more or less in consequence. Examples of this are erysipelas and diphtheria. General infections are marked by an immediately generalized disease, as in typhus fever or plague. Strictly speaking, most if not all of the so-called general infections are at first local. Among purely local infections might be named the diseases of the skin due to vegetable micro-organisms.

Entrance of Micro-organisms into the Body.—Bacteria may be inhaled or swallowed, may enter through abrasions in the mucous membrane or skin, and may be transferred *in utero* from the maternal to the fetal blood. The mode of entrance in individual diseases depends upon the nature of the bacterium, its habitat, and surrounding conditions. Some may enter in but one way; others gain access in any of the different ways. Details regarding this subject will be given in the discussion of special infections.

Animal parasites of various kinds act as causes of disease. This group of diseases is termed the *parasitic diseases* or *invasion diseases*. In some instances microparasites cause a clinical course similar to that of infectious diseases (malaria, dysentery, trichinosis); in other cases the manifestations bear little resemblance to infections.

CHAPTER II

DISORDERS OF NUTRITION AND METABOLISM

Food.—In the life of the organism certain substances are needed for growth, for the repair of tissues consumed in the wear and tear of life, and to supply heat and other energy. Among these foods are proteins, carbohydrates, fats, inorganic salts, and water. A continuance of normal existence requires more or less definite proportions of the first three and at least a sufficiency of salts and water. The amount of food and the exact proportions vary somewhat in individual cases and under varying circumstances. Voit, the pioneer in this work, found that a laboring man under ordinary conditions requires 118 gm. of protein, 56 gm. of fats, and 500 gm. of carbohydrates. This diet contains 3055 calories. Recent studies all tend to show that the amount of protein is excessive and that some reduction of Voit's figure is desirable, though the low protein figures of Chittenden and others err on the other side. The minimum figure is perhaps from 60 to 70 gm. The weight of the individual and the amount of the daily work must determine the requisite diet, 35 calories per kilo of weight being an average figure for a man doing light work. The proteins of the diet are necessary to restore tissue waste, since the organism cannot build up proteins from simpler compounds. This consumes part of the nitrogenous foodstuffs. The rest, with most of the fats and carbohydrates, is mainly useful in contributing energy.

Diminished Supply of Food; Inanition; Starvation.—Either the want of food or diseases of the digestive organs with lack of absorption may lead to insufficient nourishment. This causes a loss of body weight, as the necessary heat-producing and energy-giving substances must be supplied to maintain life, and the tissues are consumed for this purpose. During the first two to five days of starvation in previously well-nourished persons the glycogen supply of the body is largely consumed, and the amount of protein consumption is correspondingly less than on subsequent days. In prolonged starvation the average requirement of from 28 to 32 calories per kilo has been found quite constantly, and with like constancy about 13 per cent. of this energy is supplied by protein and 87 per cent. by fat. In fat persons or animals the amount of protein consumption is relatively less than in those less supplied with fat. Toward the end of long fasting periods the nitrogen elimination falls to low figures. At the same time the urea-nitrogen is especially reduced, partly on account of the reduction of exogenous proteins in the metabolism and partly on account of acidosis. (See Acid Intoxication.) The subcutaneous and other fat depots suffer first in the emaciation of starvation; later, the glandular organs, muscles,

nervous system, bones, and heart. The chlorids in the urine are regularly diminished, while calcium salts are increased in correspondence with the destruction of osseous tissue.

The functions of various organs suffer greatly: the respirations and heart action are weak, muscular exertions are reduced to a minimum, the endurance and nervous force decline, the body temperature sinks, and finally death may occur from exhaustion or secondary affections consequent upon the disturbed nutrition. (See Acid Intoxication.) The blood in starvation preserves its chemical constitution and corpuscular richness surprisingly, even after prolonged abstinence. There is probably a reduction in the total mass of blood.

Increased Supply of Food; Overfeeding.—The effect of this depends upon individual conditions, such as the amount of exercise, the surrounding temperature, and less easily demonstrable peculiarities of the individual. An excess of protein food leads to increased excretion of the end-product of its metabolism—urea. Experiments have shown that to a slight extent a reserve amount of albuminous tissue may be built up by excess of protein food. Great excess of protein eventually disturbs digestion and leads to its own discharge with the feces.

The carbohydrates and fats are broken up in the body and excreted mainly as carbonic acid and water. An excess of these foods tends to cause increased deposition of reserve fat and glycogen, which may be called upon at subsequent times of need. This deposition is a normal or physiological process and has the distinct purpose just indicated. Exceptionally in the condition called obesity the storing up of fat is inordinate and probably pathological.

Metabolism of Fat.—The fat of the body has two sources: the fat of the diet and sugar either ingested or made within the body. In the case of ingested fats the deposited fat is of like composition, and may, therefore, be widely different in its composition from the fat peculiar to the species; in the case of fat made from sugar it is always specific for the species. Thus, a dog fed upon mutton fat deposits mutton fat in his tissues, while in making fat from sugar fat peculiar to his species and differing from mutton fat is deposited. The sugar from which fat is built up may be ingested as such or may be derived from the carbohydrates, fats, or proteins of the diet or tissues.

Causes of Obesity.—Excessive ingestion of food by persons having active digestion and leading sedentary lives may occasion unusual deposition of fat. It is difficult, however, to determine the limits between physiological and pathological fatness. In some cases patients assert that the amount of food has not been excessive, and this may be actually true. Obesity in such individuals is undoubtedly pathological and due to some inherent abnormality of metabolism. A further proof of the existence of such a tendency is seen in certain families in which excessive fatness is common, even in childhood. The nature of this metabolic disorder is obscure. It has often been held that the power of oxidation is lacking, and, as a matter of course, the amount of oxygen consumed is deficient in comparison with the amount of food ingested.

This must be true or the fat could not accumulate; but it remains to be shown whether the diminished oxygen consumption is the primary cause or only an incident in the disease. Experimental investigations have shown that the basal heat production (that exhibited by the normal body when fasting and with the external temperature at 37° C.) is not exceeded in a downward direction in obesity, though the figure may be consistently low in this condition. The explanation of this circumstance may be found in the fact that in fat persons equivalent weights represent an undue amount of inactive (adipose) tissue, and that large deposits of subcutaneous fat afford an external protection against loss of heat; consistently low figures of heat requirement may, therefore, indicate, if not pathological, at least continuously low, oxidation; and it is possible that the methods of observation and the range of error of these methods may prevent the detection of slight deficiencies in oxidation that in the long run (over periods of weeks or longer) could explain fatty accumulations.

Some experiments seem to indicate retardation of oxidation though no actual reduction.

Pathological Anatomy.—The excessive adipose tissue in this condition is found in the skin and subcutaneous tissues, in the omentum and peritoneum, around the kidneys, heart, and mediastinal tissues, in the liver, and less commonly elsewhere. The amount varies from slight excess to monstrous deposits. Secondary changes in the organs (notably the heart muscle) may be due to pressure or functional inactivity.

Associated Conditions.—Fatness is more or less closely related to certain other diseases of metabolism, such as diabetes and gout. Anemia is frequently present and has sometimes been regarded as a cause, operating by reducing oxidation.

The occurrence of fatness in certain types of nervous disease, such as hysteria and idiocy, suggests a nervous perversion of fat metabolism, though possibly other conditions, for example, disease of the glands of internal secretion, may be fundamentally involved. It is well known that castration and the menopause are frequently followed by increase of fat, and certain diseases of the hypophysis and thyroid are likewise attended by obesity. There may or may not be manifest nervous symptoms in these cases.

Excessive Tissue Destruction.—This has been referred to in connection with inanition; but it may be independent of the amount of food ingested. Among the conditions in which this is observed may be mentioned fever, infectious or of other forms; chronic infectious diseases, with or without fever; tumors, especially carcinoma; intoxications of various sorts; some cases of Graves' disease, etc. In all of these conditions the fats of the body may waste as in simple inanition; but there is an early and marked tendency to consumption of the more important protein structures.

The nature of the metabolic disturbances in these cases is obscure, though it is likely that toxic substances of various sorts are the direct causes. This is most probable in the case of direct intoxications (phos-

phorus), but is also likely in other cases. In Graves' disease and carcinoma, as well as in fevers, there are doubtless poisonous substances in the blood, but whether these are the causes of the metabolic changes or not requires further study. The fact that thyroid extract is capable of causing excessive destruction of tissue in normal or obese persons is significant in this connection.

Acid Intoxication.—In the final metabolic transformation of protein there are produced ammonium, urea, kreatinin, and other nitrogenous substances. The formation of urea is still obscure in some particulars. It is certain that a large part is produced in the liver and some is formed in the glandular organs. The intermediate steps in the manufacture of urea have not been definitely determined, but it is known that the liver is capable of converting ammonium salts directly into urea, and it is probable that ammonium is an important intermediate product of protein transformation. An excess of acids in the body (either from introduction from without or production in the body) is in part neutralized by alkaline bases in the blood and tissue juices and in part by ammonium. In consequence of this consumption of ammonium the urea of the urine decreases and the ammonium salts are increased. The quantity of such salts is, therefore, in a measure an indication of the condition which has been termed "acid intoxication." When the fixed alkalies (sodium and potassium) are more or less exhausted in the neutralization of acids, symptoms of acid intoxication result. Fortunately, this is usually prevented by the abundance of ammonium, but in extreme cases of acid intoxication the ammonium does not suffice.

Experimental acid intoxication is easily produced in animals by feeding them with foods deprived of alkaline bases or by direct administration of acids. In the former case the acids (sulphuric from the sulphur of albuminous food, and phosphoric from the phosphorus) resulting from transformation of food and tissues must be neutralized by the alkalies of the body and the ammonium incidental to the process of urea formation in the liver; in the latter case there is direct excess of acid. Such acid intoxication is readily produced in herbivorous animals, as the amount of protein food is small, and in consequence but little ammonium is produced. Various nervous symptoms are observed. The animal breathes quickly, the pulse grows rapid, muscular weakness, ataxia, and tremor develop, and finally coma or collapse terminates the disease. The administration of alkalies may completely arrest the progress of the condition and full restoration may occur.

Acid Intoxication in Man.—Somewhat similar symptoms are seen in man in certain diseases in which increased elimination of ammonium, with decrease of urea and the excretion in the urine of certain organic acids, have been discovered. The assumption is warranted that these are cases of acid intoxication.

Etiology.—Among the conditions in which this occurs are fever, diabetes, carcinoma, acute yellow atrophy of the liver, narcosis, severe anemia, phosphorus-poisoning, advanced gastro-intestinal disease,

and inanition. Sometimes no discoverable cause can be detected (cryptogenic acid intoxication). Gastro-intestinal disorders are very possibly the occasion of this form of obscure acidosis. Poisons produced in the intestines may, perhaps, set in play the metabolic disturbances which terminate in overproduction of acids.

Among the acids concerned are lactic, sarcolactic, sulphuric, phosphoric, diacetic, and beta-oxybutyric. These in part combine with the fixed alkalies and with ammonium, and in part are excreted as such. Some, as sarcolactic acid, usually suffer decomposition in the body, and are, therefore, rarely met with in the urine. The important acids are oxybutyric and diacetic, and with these is frequently combined acetone.

The ketonic acids, beta-oxybutyric and aceto-acetic, are now known to be due to the combustion of fat. In normal catabolism of fat there is first a cleavage into glycerol and fatty acids. The former is converted into sugar; the latter oxidized in successive stages until the higher acids are converted into butyric acid. At this stage the process of oxidation becomes somewhat changed, and beta-oxybutyric acid, aceto-acetic acid, and, finally, through acetic and formic acid, the end-products (carbon dioxid and water) are produced. At the stage of aceto-acetic (diacetic) acid a side reaction occurs whereby acetone is formed. Normally this occurs to the extent of traces only, but when fat is burned in large quantities the acetone formation increases considerably beyond the proportionate increase of the fat consumption. In diabetes and sometimes in other conditions in which considerable fat consumption takes place, either as a result of the excess of fat catabolism or from failure of certain fermentations concerned, the conversion of beta-oxybutyric acid and aceto-acetic acid into acetone is halted or diminished and the blood is flooded with the ketone acids, which then act injuriously by abstracting bases from the tissues or as direct poisons.

There is always reduction of oxidation in cases of acid intoxication, but it is not known whether this is the primary disturbance or whether it is but an accompaniment. Experimentally it has been shown by several observers that diminution in the supply of oxygen will lead to increase of these acids. They owe their presence to excessive production and to the failure of the normal oxidation. Other substances may result from protein destruction with insufficient oxidation. Among these are the amino-acids, leucin and tyrosin, as well as lactic acid, found in the urine in phosphorus-poisoning and acute yellow atrophy of the liver as well as in other conditions.

The **symptoms** of acid intoxication in man may be quite similar to those seen in experiments upon animals. Marked dyspnea (air hunger), rapidity of the pulse, depression, stupor, and deep coma (coma carcinomatosum; diabeticum) are some of the more pronounced manifestations. The explanation of the symptoms occurring in acid intoxication is not entirely clear. The extreme dyspnea, which is one of the most characteristic symptoms, was first naturally referred to as-

phyxia; but as it has been found that the blood contains an adequate amount of oxygen and a greatly diminished quantity of CO_2 , this explanation cannot hold. It is probable, however, that the dyspnea is due to the inability of the blood to carry off carbon dioxid from the cells, in consequence of the reduction of available alkali owing to its fixation by the acids. There is thus a decrease of oxidation from the accumulation of carbon dioxid in the cells, but not asphyxia in the ordinary sense of the word. Some have believed that the symptoms of acid intoxication are due to certain as yet unknown toxins which are produced at the same time as the acids. There is no direct proof of this, and the evidence at hand would indicate that the acids in themselves, by reducing the available alkaline bases of the blood and by disturbing the metabolic processes in the cells, are sufficient to cause the symptoms.

Disorders of Protein Metabolism.—Proteins are complex bodies made up of combinations of various amino-acids in proportions differing widely in the proteins of the various tissues of the body and in those of different species. Within the gastro-intestinal tract the digestive ferments convert proteins into proteoses and peptone, and finally into the constituent amino-acids. There are thus set free the elements from which reconstruction of proteins of composition characteristic of the species in question can be effected. Some of the amino-acids from the foreign protein of the food may be unsuitable for the reconstruction of these new proteins, while some may be present in superfluous amount. These fractions are catabolized and excreted in the form of end-products. The major part is used for the resynthesis of protein. This was until recently thought to occur exclusively in the wall of the intestine, so that there should be delivered into the blood re-formed proteins similar to those of the blood. More recently it has been learned that the amino-acids are absorbed, in part at least, into the blood and utilized for rebuilding of new protein in the liver or other tissues. During youth and the growth period and after exhaustive wasting of the tissues considerable portions of the food proteins may be utilized directly for the upbuilding of the tissues. At other times only a small portion is thus utilized to repair the waste of cells and to replace dead cells. The greater part of protein food is quickly catabolized and excreted. The level of protein content of the blood is maintained very tenaciously, and in case of starvation the blood abstracts proteins from the cells to maintain the level, while as a result of overfeeding some of the protein is deposited as a storage within cells, while the larger part is quickly catabolized. There is no capacity for storage of protein comparable to the storage of carbohydrates, as glycogen in the liver and muscles, or of fat in the various areolar tissues.

The catabolism of proteins is exactly comparable to their digestion in the intestinal tract, but takes place within the cells under the influence of endotrypsin. First proteoses and peptone are formed, then amino-acids, and, finally, end-products varying somewhat with the source of the protein involved. The exogenous proteins, those derived directly

from food, are mainly excreted as urea and ammonium; the endogenous, those of the tissues of the body, when catabolized yield only small portions of the urinary urea and ammonium, and those of the muscles in particular are excreted as creatinin. The latter substance is derived from the creatin of muscles, which in turn is probably an anabolic product of amino-acids made by a special muscle metabolism.

In the normal man excess of protein feeding is speedily followed by marked increase of elimination of the end-products, urea and ammonium. Only a fractional retention occurs. In certain pathological conditions, such as nephritis and gout, considerable nitrogen retention may occur, especially in the form of non-protein nitrogenous bodies. In fasting and starvation the nitrogenous elimination falls to very low levels, in which the exogenous nitrogen end-products (urea and ammonium) are specially affected. The amount of creatinin is maintained at a quite fixed level, being reduced only to the extent of the subtraction of the relatively small amount of creatinin derived from the meat and meat extracts of diet.

Under conditions of rapid catabolism of protein, such as in leukemia, carcinoma, and internal suppurations, the proteoses and peptone may be liberated in such quantity as to be in part excreted in the urine (proteosuria, peptonuria, albumosuria). These proteoses and peptones, however, being derivatives of native protein, are non-toxic, contrasting with the toxic proteoses and peptone derived from foreign proteins in the digestive tract. Whether or not any of the latter are absorbed into the blood and excreted in the urine in pathological conditions is uncertain. In certain other conditions of rapid protein catabolism (as in autolytic destruction of liver substance—acute yellow atrophy, phosphorus-poisoning, etc.) amino-acids may be excreted in the urine.

In the catabolism of protein, under conditions in which the utilization of carbohydrates is greatly reduced, as in diabetes, considerable sugar may be an end-product. This is derived from the amino-acids, which lose their NH_2 by a process of deaminization and yield oxy-fatty acids, which are finally converted into dextrose. This process accounts for much of the persistent dextrosuria of severe cases of diabetes after the glycogen storage has been exhausted and the diet has been deprived of all carbohydrate matter.

Creatinin elimination in the urine may be utilized as an indication of the state of muscle metabolism. In cases of rapid muscular waste from fever or other causes an excessive output of creatinin is met with; and in certain extreme cases creatin itself—the substance in muscle from which creatinin is derived—is thus excreted, probably as an expression of failure of conversion into creatinin. In muscular dystrophies the elimination of creatinin may be decreased.

Disorders of Purin Metabolism.—By purin metabolism is meant the metabolism of cellular nuclei. The nuclei contain nucleoproteins which are combinations of globulin and nucleic acid, the latter being composed of phosphoric acid, pentose-sugar, and a base, either purin or pyrimidin. The important purin bases are the aminopurins, adenin and guanin,

and the oxypurins, hypoxanthin and xanthin. In the normal purin catabolism there is first a separation of the globulin and nucleic acid, and then, under the influence of special enzymes, the latter is broken up into its components and the purin bases deaminized and oxidized to uric acid. In the final urinary excretion both purin bases and uric acid are present, so that the catabolism does not wholly proceed to the end-product. Under ordinary conditions of diet the urine contains more purin of exogenous than of endogenous origin. The foods that yield this are such cellular gland foods as thymus, pancreas, liver and kidney, and, to a less extent, muscle (meat); leguminous vegetables; and coffee, tea, and cocoa. On a purin-free diet the excretion falls to a low level of fair constancy. Apparently the exogenous purins are excreted *in toto*, no part being utilized in the anabolism of nucleic acid. To a certain extent uric acid is oxidized in the body to form urea and is excreted as such.

Under normal conditions the blood contains from 0.5 to 1.0 mg. of uric acid in 100 c.cm. Under certain circumstances this quantity may rise to 8 or 10 mg. either temporarily or for longer periods. Among these conditions are chronic nephritis, gout, lead-poisoning, after heavy feeding on purin foods, during resolution of pneumonia, in sepsis, etc. In the last three of the conditions named there is excessive cellular metabolism and consequently temporary overproduction of purin bodies. In the first three the higher level of uric acid is probably due to some alteration of the renal permeability which maintains a higher threshold for the elimination (see below), rather than to any increased production of uric acid.

Gout.—In its typical form gout is a paroxysmal disease marked by deposits of urates in the joints and other structures, and by coincident or consequent inflammatory disturbances. There are many varieties, however, of irregular gout in which the paroxysms may be partly or wholly wanting, and in which the disease takes the form of a general systemic disorder, or of organic maladies of various sorts.

Etiology.—Gout is essentially a hereditary diathetic affection, the heredity not rarely being polymorphous. By this is meant that in certain families gout and other diseases, such as obesity, diabetes, and arterial sclerosis, may occur interchangeably. Gout usually develops in the later years of life, and among the contributing causes are the use of alcohol, overeating, sedentary life, and chronic lead-poisoning.

Pathological Anatomy.—The conspicuous anatomical lesions are those of the joints, and consist of the deposit of urate of sodium in the cartilages and connective tissue, and secondary inflammatory changes. The latter may cause great distortion and fibrous overgrowth. Similar urate deposits may occur in the cartilages of the ear, eye and nose, and in the subcutaneous connective tissue or elsewhere. These deposits, called the gouty *tophi*, may subsequently disappear by absorption or by discharging through the skin. Cirrhosis in various organs and tissues of the body frequently occurs in the course of gout. Among these the cirrhotic or gouty kidney is most important. Atheroma, cirrhosis of

the liver, hypertrophy and fibroid change in the heart, and chronic valvular disease are also frequent.

Pathogenesis.—For a long time some disorder in the formation and excretion of uric acid has been held responsible for the manifestations of gout.

Garrod first demonstrated an excess of uric acid in the blood, and recent exact chemical studies have confirmed this observation. There are, however, as has been shown, diseases, such as leukemia, nephritis, and pneumonia, in which excess of uric acid in the blood occurs without any of the results seen in gout. It is possible, of course, that the accumulation in the blood may be due to different causes in these conditions, but it is evident that other factors beside the mere presence of excessive uric acid are operative in gout.

The excretion of uric acid in the urine is found reduced just before an acute paroxysm of gout, increases above the normal during the attack, and then falls to about the normal. In chronic cases without attacks the excretion is about normal. The increased quantity in the blood might then be due to increased production or to a reduced transformation to simpler metabolic products. Neither of these explanations seems justified. At present the more probable reason seems to be a change in renal permeability (without any special renal lesion), as a result of which the threshold of excretion is raised. The reduction of uric acid before attacks has been attributed to the deposition of acid urate of soda in the joints and elsewhere, though the amount of uric acid in all the deposits falls far short of that which could explain this. Possibly changes in diet or intestinal absorption may play a part in this reduction.

The pathogenesis of the urate deposits remains obscure. Ebstein first insisted that local necrosis, itself perhaps the result of excess of uric acid in the blood, is the direct occasion for the deposits, and some recent authorities believe that a primary and essentially gouty local inflammation invites urate deposits, the uric acid itself having no importance in the first condition. Experiments have, however, shown that uric acid is capable of causing local inflammatory lesions. Traumatism and circulatory conditions may play a part in localizing gouty precipitations.

Possibly the conditions in which uric acid is held in solution in the blood may differ in gout from those in health and other diseases.

Studies of the general metabolism in gout show a uniform tendency to nitrogen retention, apart from any possible reduction in uric acid excretion. There is also a reduction of intestinal absorption, with increased excretion of indican.

Diseases of Carbohydrate Metabolism.—The carbohydrates of the diet are converted into dextrose or glucose before absorption, this conversion being accomplished by salivary and gastro-intestinal enzymes. After absorption into the blood the dextrose is converted into glycogen and stored in the liver cells, or, in cases of excess above the hepatic capacity of storage, in the muscles. Normally, there is a storage

of glycogen sufficient to supply the nutritional needs for as much as five days; in fasting experiments it has been clear that the nutritional needs have been supplied by glycogen during the first few days. It has been a subject of much investigation and discussion whether or not other sources of sugar exist besides the ingested carbohydrates. Recent studies have shown beyond doubt that the amino-acids of protein catabolism may furnish considerable quantities of sugar by deaminization and subsequent conversion of the oxyfatty acids into glucose. In severe diabetes this may be a noteworthy source of sugar. It is conceivable that the glycerole derived from the splitting of fat may also furnish sugar, and this derivation seems probable, though it has not been definitely proved.

The blood maintains a fairly constant sugar content under normal conditions—the amount being about 0.080 gm. per 100 c.cm. With normal quantities of sugar in the blood, glucose ordinarily fails to appear in the urine because a certain threshold of retention prevents its excretion through the kidneys. When the blood sugar is reduced the glycogen stores of the liver will replace the loss. There is thus maintained a fairly constant level of sugar concentration. When the sugar reaches a high level—beyond the storage capacities for glycogen in the liver and muscles—the excess is deposited as fat in the areolar tissues. Still higher levels of sugar concentration may exceed the capacity for storage as glycogen or fat and the threshold of renal permeability. Glucosuria then results.

Ultimately, sugar is oxidized in the muscles and converted into CO_2 and H_2O . The glycogen stores in the liver are in cases of need converted into dextrose, delivered to the blood, and finally burned in the muscles. The glycogen stores of the muscles are not available for maintaining the sugar content of the blood, but are utilized only by oxidation in the muscles themselves.

Hyperglucemia.—Excess of blood sugar—a condition termed “hyperglucemia”—may be a temporary result of ingestion of starches or sugar, or a more lasting condition in certain diseases (diabetes, thyroid diseases, hypophysis diseases, cancer). Under normal circumstances the liver is capable of storing as glycogen any amount of sugar derived from mixed or starchy diet. The processes of digestion and absorption do not furnish to the blood amounts of sugar sufficient to overbalance the storage capacity of the liver. Pathologically, the liver may fail to store the sugar and the excess in the blood may occasion excretion in the urine (hyperglucemia-glucosuria). In normal cases the blood sugar after a meal may increase in one or one and one-half hours to 100 or 125 mg. per cubic centimeter, but the amount quickly falls to its former level.

Alimentary Glucosuria.—When large quantities of sugar (dextrose, fructose, or other forms) are ingested the capacity for storage may be exceeded and glucose may appear in the urine. Under certain pathological circumstances (diseases of the liver, alcoholism, thyroid disease) the ingestion of relatively small amounts of sugars may be followed by glucosuria (glucosuria *e saccharo*), and even starch ingestion may occasion

a like result (glucosuria *ex amylo*). Sometimes the glucosuria in such cases may perhaps be due to the fact that the liver is already stored to its capacity and cannot accommodate additional deposits of glycogen.

Glucosuria Due to Excessive Hepatic Glycolysis.—Under certain circumstances the liver converts its stored glycogen into glucose so rapidly that hyperglucemia and glucosuria result. This seems to be the explanation of the glucosuria occasioned by Claude Bernard's classical experiment of puncture of the medulla and by certain poisons such as chloral, morphin, antipyrin, etc.

General Scheme of Possible Causes of Glucosuria

1. Alimentary—excessive ingestion of starches and sugars beyond the storage capacity of liver and muscles.
2. Defective hepatic glycogenesis—incapacity of the liver to transform and store as glycogen.
3. Excessive hepatic glycolysis—too rapid conversion of glycogen into glucose.
4. Defective muscular glycogenesis—incapacity of the muscles to transform sugar and store as glycogen.
5. Excessive muscular glycolysis—conversion of muscle glycogen into sugar and excretion as such.
6. Inability of the muscles to oxidize sugar. (See Diabetes.)
7. Increased renal permeability for sugar. (See Diabetes.)

Clinical Causes of Glucosuria.—Glucose appears in the urine under a variety of conditions, including dietary excesses; various infectious diseases; intoxications (morphin, strychnin, chloral, acetanilid, etc.); concussion, injury and diseases of the central nervous system; after convulsions; in thyroid and hypophysis diseases, and in diabetes mellitus.

Diabetes mellitus is a disease in which polyuria and glucosuria are marked symptoms. It is not improbable that the term includes disorders of quite different sorts, but no certain differentiation of such is possible at the present time. A *mild* and a *severe* form are distinguished, and these present some striking differences, to which reference will be made below.

Etiology.—Diabetes is frequently a hereditary disease, occurring in families in which the same disease or obesity and gout have occurred. The Jews seem particularly liable to it. Overeating, sedentary life, and gout are causes of some importance, especially of the milder form. Sometimes abnormal conditions of the nervous system may be the underlying cause. Among these are functional depressions, as in cases of excessive grief; traumatic injuries with concussion of the brain; and local diseases at the base of the brain in the vicinity of the medulla. Disease of the pancreas is the probable cause in many cases, and may possibly play a part in all cases, though demonstrable lesions of the pancreas are not present in all. Diabetes may occur in the young or after middle life, the milder cases more frequently occurring at the latter period.

Pathogenesis.—In the milder cases of diabetes the same explanation may be applicable as that given for glucosuria, viz., the liver and muscles do not store up the carbohydrates carried to them, and the excess of sugar is not burned up in the tissues. Hyperglucemia with consequent glucosuria results. In these cases the withdrawal of carbohydrate food or temporary abstinence from all food causes disappearance of the glucosuria. There is, however, the fundamental difference between mere glucosuria and true diabetes that in the former the capacity to burn sugar is unimpaired, while in the latter even in mild cases this function is more or less disturbed.

In severe diabetes sugar continues to appear in the urine in spite of complete abstinence from starches or sugars. This is explained by the conversion of glycogen into sugar and when this supply is exhausted by the formation of sugar from the amino-acids of protein catabolism, and possibly also by conversion of the glycerol of fat catabolism into sugar. In normal individuals, and even in those suffering with mild diabetes, any sugar thus liberated is burned in the tissues. Glucosuria does not, therefore, occur. Severe and mild diabetes differ only in degree: in one case the power to consume sugars is greatly deficient, in the other only moderately so.

The nature of the metabolic disturbances that lead to this inability to dispose of carbohydrates is still very obscure. The influence of the nervous system is undoubted. Reference may here be made to the occurrence of diabetes after puncture of certain parts of the brain (medulla). Very possibly this experiment as well as certain clinical causes of diabetes act by increasing hepatic glycolysis, and in consequence by flooding the blood with sugar.

Older pathological studies showed that diseases of the pancreas are frequently associated with diabetes, and recent experimental investigations emphasize this relationship. Total extirpation of the pancreas in the lower animals causes diabetes. The relationship between the pancreas and diabetes has not been certainly established. Formerly Lepine and others believed that the pancreas elaborates a "glycolytic ferment," absence of which in cases of disease of the pancreas would occasion accumulation of sugar in the blood and consequent glucosuria. More recently it has been found that a coöperation of muscle extracts with pancreatic extracts is necessary to the destruction of sugar, from which it would appear that normally pancreatic secretions are carried to the muscles and activate the process of oxidation of sugar. It seems to have been established that the final oxidation of sugar occurs in the muscles and not in the liver. The secretion of the pancreas involved in this function is doubtless a product of the islands of Langerhans. (See Pancreas.) Other glands of internal secretion seem to have some relation to the pancreas and perhaps to the muscles in the development of diabetes. It is known that epinephrin when injected into the body may occasion glucosuria, and diseases of the hypophysis cerebri also occasion glucosuria. The adrenals and the hypophysis may act by restraining normal pancreatic function.

Renal Glucosuria.—Experimentally, glucosuria may be produced by injections of phloridzin, a glucoside which is composed of phloretin and glucose. Formerly the explanation of the glucosuria resulting from injections of phloridzin was as follows: Splitting of the glucoside into glucose and phloretin was supposed to occur in the kidneys, the glucose being excreted as such, and the phloretin returning to the circulation and reuniting with glucose in the liver or elsewhere to form new phloridzin, which underwent the same process as that first administered. Careful investigations, however, have shown that phloretin itself does not act in this manner, and that the cleavage of phloridzin in the kidney, as assumed, is improbable. At the present time the more trustworthy explanation of phloridzin glucosuria is that it causes some change in renal permeability which occasions active excretion of sugar when the sugar concentration of the blood is at or even below the normal level. It was early recognized that in cases of phloridzin glucosuria the amount of sugar in the blood is not above normal, and this fact was one of the confusing conditions that required explanation. In the light of present knowledge it would seem that the blood tends to maintain its normal sugar content by obtaining glucose from the liver and the diet, while the lowered renal threshold allows sugar to escape in the urine. The process of excretion of the sugar is probably not an entirely passive one, to be regarded as a mere overflow when the concentration of the sugar in the blood is above the limits of renal retention; more likely there is an active eliminative process in the kidneys that becomes effective when the sugar reaches a certain concentration. It is believed by many that certain cases of glucosuria in man are due to a similar disorder of renal permeability, and in particular the glucosuria associated with gout, arteriosclerosis, and chronic nephritis may be explainable on this basis. It is impossible at present to make more positive statements.

The view that diabetes is due to increased formation of sugar has been definitely disproved.

Metabolism in Diabetes.—The essential metabolic disturbance in diabetes is the inability of the body to consume and utilize sugar. In mild cases this is a moderately developed defect; in severe diabetes it is more and more pronounced, though probably never absolute. As a result the sugar concentration of the blood is increased and amounts to from 0.120 to 0.180 gm. per 100 cubic centimeters, with even higher figures soon after ingestion of carbohydrates or sugar. The inability to utilize sugar causes increased consumption of fat and proteins and leads to emaciation. In mild cases and for a time in severe diabetes overfeeding with fats and proteins may prevent loss of weight from destruction of the fats and proteins of the body, but eventually this protection of the tissues fails to be effective. There is always a tendency to excessive destruction of proteins and nitrogenous loss, as the diabetic is unable to utilize carbohydrates to protect the proteins. The fats also are consumed to an excessive degree and their oxidation tends to be abnormal, as a result of which the ketone acids and acetone are formed in excessive amounts. (See Acid Intoxication.) Increased elimination of

ammonium and other bases (alkalies, calcium, magnesium) are expressive of the overproduction of acids and their neutralization by the bases in question.

Pathological Anatomy.—Aside from the lesions already referred to as in some way related to the causation of the disease, there are found pathological changes of various kinds that result from it. The lesions of gout (arteriosclerosis and cirrhotic kidneys) may be of the nature of mere concomitants, but similar lesions may be direct results of diabetes. Renal diseases are of peculiar interest. Late in diabetes albuminuria frequently develops and interstitial nephritis may follow. When this occurs the glucosuria and other symptoms of diabetes sometimes subside. Changes in the liver (cirrhosis) have often been found, and have been regarded as causative in some cases. A peculiar form of diabetes with hepatic disease and general staining (hemochromatosis) of the skin and other tissues has been described under the title *diabète bronzé*. Skin eruptions (eczema, furuncles, carbuncles) are frequent in certain forms of diabetes, and gangrene of the extremities is common. Pneumonia and pulmonary tuberculosis are among the frequent developments of late stages of the disease. Chronic endocarditis, neuritis, and cataract are not uncommon lesions.

Pentosuria.—Pentose (a sugar containing five carbon atoms) is found normally in the nuclei of cells, the total amount in the whole body being estimated as approximately 20 gm. Occasionally pentosuria is met with either in combination with glucose in diabetes or as an independent condition unattended by symptoms and tending to occur in several members of a family. It is certainly not due to the ingestion of pentoses in the diet, and is probably an independent metabolic disorder sometimes associated with diabetes, but at other times wholly independent.

Oxaluria.—This term is, strictly speaking, applicable only to increase of oxalic acid in the urine, but is usually employed for cases in which crystals of oxalate of lime are found abundant in the urine. The normal maximum of oxalic acid is 20 mgr. for twenty-four hours. True oxaluria determined by chemical estimation of the total excretion of oxalic acid has been found in jaundice and in some cases of diabetes. The source of oxalic acid in the urine is still somewhat in doubt. Several investigators claim to have found that the older view regarding its presence in excess in the urine following certain kinds of vegetable diet is erroneous, and that there is no such thing as "alimentary oxaluria." The weight of opinion, however, still favors the older view. There is some experimental evidence for the belief that intestinal fermentation is an important factor in the formation of oxalic acid. While this may be true, there seems little doubt but that the oxidation of uric acid accounts for the presence of much of the oxalic acid in the urine, and that nucleins and nucleo-albumin are, therefore, important sources of derivation. The authors who have argued in favor of a specific disease marked by nervous symptoms and oxaluria based their observations on the presence of an excess of oxalate sediment, rather than on chemical examinations. Increased sediment occurs in certain instances of gout in which the oxalates alternate with uric acid or coexist with this. In these cases, as in cases of oxalate calculus in the kidney or bladder, the important causative factor is most probably some alteration in the constitution of the urine, such as conversion of monosodic phosphate into the disodic phosphate, that reduces the solvent power of the urine for oxalate of lime.

Metabolism of Phosphorus.—Phosphorus exists in the body in the nuclei of cells in combination as nucleic acid, in the bones as phosphates, and in the lipoids of the nervous system. The phosphorus of food is absorbed as phosphoric acid, which combines with sodium, calcium, and magnesium, and from these combinations is

utilized in the anabolism of phosphatic compounds of the tissues. The excretion of phosphorus takes place through the kidneys and intestinal tract. Phosphorus of the diet may fail of normal absorption in the presence of excess of calcium, which, combining with phosphoric acid, is discharged in the feces. Under ordinary conditions the phosphorus of the urine, like purin output, is a measure of nucleic metabolism. Excess of phosphorus elimination may be encountered in cases of destruction of bone.

Phosphaturia.—This term should be restricted to increased excretion of phosphoric acid rather than to the presence of increased phosphate sediment in the urine. The latter may be due simply to want of acidity of the urine. The daily maximum of phosphoric acid with ordinary diet is from 3.5 to 4 gm. The term "phosphaturia" might also be applied to cases in which no absolute excess of phosphoric acid is found, but in which this substance is relatively in excess when compared with the excretion of nitrogen. The normal proportions are from 17 to 20 parts of phosphoric acid for 100 parts of nitrogen. Phosphaturia in the sense just described has been found in some cases of inanition. Decided increase in the phosphatic excretion, absolute as well as relative, occurs in some cases of diabetes; also in cases of tuberculosis and disease of the bones, such as *ostitis* and *osteomyelitis*. In considering the question of phosphatic excretion in the urine it is important to remember that the greatest portion of phosphoric acid is derived from the food, only minor quantities coming from the metabolic consumption of tissues. Further, it must be remembered that much of the phosphoric acid of metabolism is excreted through the bowel. Recent observations show that when there is some intestinal disorder preventing excretion of calcium from the intestines there may be excess of phosphoric excretion in the urine in combination with calcium. The term *diabetes phosphaticus* has been used by Teissier for phosphaturia in the sense of increased total excretion, and four varieties have been described: (a) cases with polyuria and marked nervous symptoms; (b) cases preceding or accompanying pulmonary diseases, especially tuberculosis; (c) cases in which phosphaturia alternates with or coexists with glycosuria; and (d) cases in which oxaluria, polyuria, and slight albuminuria are present and in which there is some relationship with gout.

The nature of the metabolic disturbances in phosphaturia are obscure. Sometimes the disorder of metabolism seems to be merely quantitative; in other cases, doubtless qualitative.

FEVER

Definition.—It is not easy to define this term accurately, though we may regard as fever a condition in which the temperature of the body is elevated above the normal (98.4° F.; 37° C.) and in which the tissue-metabolism is altered in the direction of increased consumption. There are cases in which the latter is insignificant or wanting, and there are other instances in which the temperature remains normal or subnormal under influences that ordinarily provoke fever. It is doubtful whether mere elevation of temperature, such as occurs in experimental injury of certain parts of the brain, constitutes fever; but unquestionably it would be improper to apply this term to conditions of excessive tissue destruction without elevation of temperature.

Nature.—It is important, first, to consider the regulation of the temperature in health. In the normal individual heat is produced in the body by constant oxidation and other metabolic activities, and the excess is dissipated by radiation from the surface and the heating or evaporation of excreta. These processes of *heat production* and *heat dissipation* are regulated in an orderly manner under the influence of the nervous system. Special centers for the production, dissipation, and

regulation of heat have been described by the physiologists, though their location and method of operation still remain in doubt. Whatever the exact mechanism may be, it is quite certain that in some way the nervous system exercises a control over production and discharge of heat.

The excessive heat of fever may conceivably be due to excess of heat production, to diminution of the dissipation, to both of these conditions, or to increase of both with greater excess of production. In most instances of fever in man it appears that production and dissipation are both increased, though the latter is insufficient. At the onset heat dissipation may for a time be diminished. The increased production results from increased oxidation and other metabolic processes. A study of the respiratory exchange of gases shows that oxygen is consumed in greater quantity than normally, and the quantity of CO_2 is correspondingly increased. The excess may amount to as much as 20 per cent., but in part this increased oxidation is due to the stimulation of muscular contractions in rigor, etc. Investigation of the excreta shows at the same time evidences of more or less rapid and extensive tissue waste. The quantity of nitrogen eliminated is in excess of that consumed in the food, and wasting of the tissues results. The albuminous elements suffer particularly in the metabolic wasting, the decrease of fat being more especially dependent on insufficiency of food.

Etiology.—The causes of fever doubtless vary greatly. Direct exposure to heat does not affect the temperature more than a fraction of a degree in healthy persons, unless the surrounding temperature is very great. Ordinarily the heat-regulating mechanism maintains a proper adjustment. Excessive heat may, however, bring on fever, as in the case of sunstroke. Here, it has been held that the heat leads to direct disturbances of the regulating apparatus in the central nervous system; but recent investigations seem to show that there are first produced toxic substances which secondarily influence the heat-centers of the brain. In another class of cases still more direct disturbance of heat regulation seems to occasion fever. Among these cases are the instances of fever in hysteria and other nervous diseases.

In the great majority of cases of fever it is quite certain that toxic substances are the cause of the febrile disturbances. These substances may be of quite different sorts. In the case of infections it is known that certain substances contained within the bacteria themselves may cause fever, and that products of the growth of the micro-organisms may have the same effect. These substances are probably of albuminous nature. Other albuminous bodies resulting from normal or disturbed metabolism, independent of the action of bacteria, such as albumoses, peptone, tissue-fibrinogen, etc., may be equally potent; and various ferments, such as pepsin, fibrin-ferment, diastase, etc., are known to have the same power. These facts explain the multiplicity of causes capable of producing fever, as any chemical, mechanical, or bacterial injury of the tissues may liberate toxic substances, which in turn act upon the nervous system and occasion the phenomena of fever.

Pathological Physiology.—Fever is accompanied by or leads to a variety of disorders. The appetite is lost, there is excessive thirst, emaciation is habitual, and the functions of the various organs are more or less disturbed. To a large extent these results are doubtless due to the presence of toxic substances in the blood and to other changes in this fluid. There is always a tendency to inspissation of the blood, the number of corpuscles being augmented (relatively) and the specific gravity increasing. This is not, however, invariably the case, as destruction of the solid matters of the blood may exceed the loss of liquid. The alkalinity of the blood is more or less reduced by the production of various acids in the increased tissue destruction. A common and possibly characteristic metabolic process is the hydration of the albuminous tissues with formation of albumoses. There is little accurate knowledge of the toxic substances in the blood. The original poisons that caused the fever may be toxic for the entire organism, and other poisons may be produced by the elevation of temperature and the disturbed metabolism.

Pathological Anatomy.—Definite morbid changes may occur in the various tissues of the body, notably the muscles, heart, liver, and kidneys. Among these changes are cloudy swelling, fatty degeneration, and coagulation necrosis. It is unlikely that these changes are the direct result of the increased temperature. More probably they result from the action of toxic substances generated in the course of the fever.

Conservative Effects of Fever.—While fever occasions many disturbances and leads to various pathological consequences, it is not improbable that there is a certain measure of usefulness in it. Some authors have called attention to the fact that rapid reduction of the temperature under the influence of antipyretics is often followed by harmful consequences. This does not necessarily prove the usefulness of the fever, as the antipyretics are all capable of harm in themselves. A more definite proof of the uses of fever is that obtained by subjecting infected animals to high temperatures or to febrile conditions, and then studying the progress of the infection. Under these circumstances it has been found that the course of various infections, such as with the *Diplococcus pneumoniae*, the bacillus of typhoid fever, and other organisms, is much milder and the consequences less serious than in animals not placed under the same conditions. These results agree very well with experiments with bacteria outside the animal body. For example, it is known that many of the bacteria are influenced unfavorably in their growth and virulence by excessive temperatures (104° to 107.6° F.; 40° to 42° C.). Whether in the body the temperature affects the microorganisms directly or indirectly through the production of antitoxic substances, or in other ways, remains unsettled. It is not unlikely that increased circulation and respiration favor the elimination of the toxins that cause the fever. Increased toxicity of the urine has been found, but the methods employed are open to criticism.

CHAPTER III

DISTURBANCES OF THE CIRCULATION OF THE BLOOD

GENERAL DISTURBANCES

THE circulation of the blood is maintained by the rhythmic contractions of the auricles and ventricles of the heart, aided by the elasticity of the arteries; by the compression of the veins by the muscles; and by the suction of the inspiratory movements of the chest.

General disturbances of the circulation result from lessened or excessive heart power, from arterial disturbances, or from changes in the quantity or character of the blood. Muscular and respiratory weakness may be contributing causes.

Weak Heart.—There are various forms of heart disease that may lead to disordered circulation. The muscle itself may be weakened from overstrain, the fevers or other diseases, the action of poisons or insufficient nourishment, as in the anemias or from narrowing of the coronary artery. The muscle may be soft and cloudy, fatty, or hardened by sclerotic changes. There may be no evident muscular disease, but merely functional weakness. The valves or orifices of the heart may be diseased, and regurgitation or obstruction of the blood-flow results. Sometimes blood-clots form within the heart and similarly cause obstruction of the current. Finally, pericardial effusions or adhesions or tumors pressing upon the heart may seriously disturb its action.

The result of the weakened state of the heart must be the accumulation of blood in the venous system. The place of engorgement depends upon the part of the heart specially weakened. If the left ventricle fails, the blood backs into the left auricle and the lungs. As long as the right heart maintains its power the venous congestion goes no further; but when this fails, repletion of the right auricle and of the systemic veins ensues. When the right heart is first at fault, general venous congestion is an earlier manifestation. In all cases the arterial pressure falls and the blood-current is slowed, whereas the venous pressure is increased.

Sudden and complete failure of the heart causes anemia of the brain and syncope, which may prove fatal if not instantly relieved.

Hypostatic Congestion.—In cases of serious weakness of the heart, in which it is quite unable to maintain an active circulation, the blood tends by the force of gravity to sink to dependent parts. This condition is known as hypostatic congestion. It occurs very frequently in low fevers and quite commonly just before slow death resulting from any cause. Dilatation of the vessels from vasomotor paresis, general muscular weakness, and the failure of vigorous inspiratory efforts are secondary causes.

The blood accumulates in the skin of the back, especially about the buttocks. The skin is of a livid color, but is bloodless over the bony points; the tissues tend to become sodden from transudation of liquid from the blood-vessels. Sloughing and gangrene (bed-sores) may result. Internally, hypostatic congestion affects the lungs particularly, and a form of pneumonia may follow.

Postmortem lividity is allied to hypostatic congestion. After death the blood gravitates to the dependent parts and accumulates in the veins, as the arteries contract when the heart-action ceases.

Overaction of the heart is less frequent than weakness. Temporary overaction occasions increased activity of the circulation and elevation of blood-pressure, sometimes sufficient to cause hemorrhage. More prolonged overaction due to overwork, to excessive feeding, or to nervous stimulation, as in Graves' disease, causes hypertrophy of the left ventricle, and later of the whole organ. In consequence the circulation may be more or less permanently overactive.

Arterial Disorders.—Both organic and nervous disturbances are important. Of the *organic disturbances* the most frequent is sclerosis of the arteries, which offers a constant impediment to the arterial circulation. Hypertrophy of the heart overcomes the obstacle, but when the heart fails venous congestion and dropsy ensue. Sclerosis may also affect the veins, but much less commonly. Local diseases of the aorta, as congenital narrowing, compression by enlarged glands or tumors, aneurysms, and blood-clots may obstruct the flow of blood to the arteries, and thereby cause stagnation of the blood in the heart, lungs, and venous system.

Vasomotor disturbances are dependent upon the nervous system. Under the influence of certain diseases of the nervous system or of poisons (as carbonic acid gas in asphyxia) acting locally on the vessels or upon the vasomotor center in the brain, contraction of the smaller arterioles occurs; and in consequence the blood-pressure is greatly elevated, the heart is impeded, and venous congestion results. On the other hand, the arterioles may distend from vasomotor paresis, the blood-pressure falls, and unless the heart is active there is a tendency to hypostatic congestion.

Changes in the Blood.—Increase and decrease of the quantity of the blood are generally merely passing conditions to which the circulation readily adapts itself by dilatation or contraction of the vessels. Sudden losses of blood, if large, may be fatal by syncope. Smaller losses are soon repaired by absorption of water from the tissues and by regeneration of blood. Increase in the quantity of the blood by ingestion of liquids never disturbs the circulation greatly. Rapid excretion soon reduces the quantity to the normal.

Changes in the character of the blood may affect its circulation. The accumulation of carbonic acid and probably other effete products of tissue change impede the flow by exciting vasomotor contraction. This is probably brought about by the action of the poisons on the terminal nerve-filaments in the blood-vessels or directly on the walls of

the vessels. This is the best explanation of the increase of pressure in cases of Bright's disease without arteriosclerosis. The poisons in this case are quite possibly retained substances which the damaged kidney cannot excrete.

The changes in pressure cited above may be largely due to changes in the viscosity of the blood. In general, anything which increases the cellular content or molecular concentration increases pressure, while the reverse is naturally the case. The chromaffin system, particularly of the adrenals, seems to have a stimulating effect upon blood-pressure. It is believed by some observers that an overproduction of epinephrin is responsible for chronic arterial disease.

LOCAL ANEMIA

Local anemia or ischemia is the condition in which a tissue contains less than its proper quantity of blood. This may be *direct* when it results from causes obstructing the flow into the arteries, or *collateral* when it is due to withdrawal of blood into hyperemic areas in other parts of the body. Of the causes acting directly, pressure is the most frequent. There may be general pressure upon an organ or localized area of the

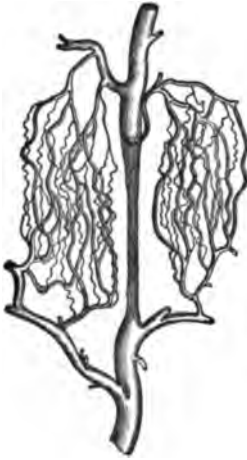


Fig. 1.—Anastomoses three months after ligation of the femoral artery of a dog (Porta).

body, as in the application of elastic bandages; or pressure upon the vessels within the tissue itself, as in amyloid disease, the amyloid substance compressing the arteries and capillaries, or there may be direct compression of an artery by tumors. The circulation in an artery may be impeded by sclerosis of the vessel walls and by emboli or thrombi within the vessel. Local anemia of moderate or even severe grade may be due to nervous influences acting through the vasomotor system, as in the earlier manifestations of Raynaud's disease. Collateral anemia is well illustrated by the anemia of the brain occurring in animals in which the splanchnic nerves have been cut, with the consequent production of abdominal hyperemia. When ischemia is due to obstruction of a single vessel the circulation is generally soon restored by collateral anastomosis; the collateral vessels sometimes reach considerable

dimensions (Fig. 1). When an artery which has few anastomoses and which soon splits up into capillaries is obstructed the phenomena of infarction (see page 66) ensue.

An anemic area is pale, reduced in size and temperature, and functionally less active than normal. If the condition persists, fatty degeneration and necrosis results. When a severe local anemia is relieved it is apt to be followed by hyperemia of the same area, due to exhaustion or degenerative weakness of the vessel walls.

LOCAL HYPEREMIA

Local hyperemia is increase in the quantity of blood in a part of the body. This may be due to increase of the flow to that part, or to obstruction of the outflow. The former is called *active* or *arterial hyperemia* or *congestion*; the latter, *passive* or *venous hyperemia*.

Active hyperemia occurs in organs during periods of functional activity, the increased blood-supply here being due to increased demand for nutrition. Pathologically, active hyperemia is due to causes which lead to dilatation of the arteries of a certain part. This dilatation may be due to influences acting through the vasomotor nervous system or to local affections of the vessel walls. The vasomotor nervous system may be affected at its center in the medulla or peripherally. The latter is seen when the sympathetic nerves, which contain vasoconstrictor fibers, are severed or compressed by tumors, the vessel walls thereby becoming paralyzed (*neuromparalytic hyperemia*). The superficial congestive hyperemia in fevers is probably due to the central vasomotor action of the toxic causes of fever. On the other hand, the vasodilator fibers in the spinal nerves may be stimulated, as in certain cases of neuritis, with a similar result (*neurotonic hyperemia*). Direct injury to the vessel walls by heat, traumatism, inflammation, chemicals, or by the vascular fatigue following temporary stoppage of the circulation is a frequent cause.

Active hyperemia is spoken of as *collateral* when anemia in one part leads to overfilling of the vessels of an adjoining or even distant part.

The hyperemic area is bright red in color, the temperature is elevated, and there is slight swelling, due to the increase of blood in the part and transudation of serum into the tissues. After death the distended arteries and capillaries may contract and the part grows paler. Arterial hyperemia is one of the phenomena of beginning inflammation, and in any case if prolonged may terminate in inflammation. Functional activity is increased by moderate congestions.

Passive hyperemia is due to impediments to the outflow of the blood through the veins. This may be brought about by compression of veins by tumors, by thickening of their walls, or by thrombi within. Little disturbance results from obstruction of a small vein, because of the freedom of collateral circulation, provided the heart is active. In cases of weak heart-power, however, slight obstructions may determine local venous hyperemia, or by gravity alone the blood may accumulate in dependent parts. The latter constitutes *hypostatic congestion*.

Areas the seat of passive hyperemia are dark red (*cyanosis*) and lowered in temperature. The veins are distended, and very soon the watery elements of the blood transude and the part becomes edematous and swollen. In severe cases red blood-corpuscles escape by diapedesis.

This occurs in the small veins and capillaries, but not in the arteries. In consequence of the increased intravascular pressure the red corpuscles are pushed through the wall of the vessel at the angular

junction of adjacent endothelial cells. At these points the cement substance is found in greater abundance than along the borders of the cells, and the escape of the corpuscle takes place through the semisolid cement substance.

Later fatty degeneration results from the imperfect nutrition of the tissues; or even necrosis and gangrene may occur. In long-continued moderate passive hyperemia overgrowth of connective tissue, due either to direct irritation or a replacement process, or both, and pigmentation of the tissue by broken-down blood-corpuscles is observed (brown induration).



Fig. 2.—Stasis of blood in the superficial vessels in a case of valvular disease and heart failure (modified from Ziegler).

Complete stoppage of the circulation in a localized area is called *stasis* (Fig. 2). This may be an extreme grade of passive hyperemia. The blood-corpuscles accumulate in the small vessels (arteries, capillaries, and veins), and the plasma is slowly pressed through the vessel wall or onward in the vessel. There results a filling of the vessel with a homogeneous red material, which is composed of the red corpuscles so closely packed as to be indistinguishable. On relief of the stasis the corpuscles become free again. Stasis may also be produced by chemical agents which rapidly withdraw the plasma from the vessels, leaving the corpuscles unable

to circulate; or similarly by rapid evaporation of the liquor sanguinis from internal structures (as the peritoneum) exposed to the air.

Passive congestion of any grade and stasis interfere with functional activity in two ways: by the reduction of nutrition of the cells and by the pressure exercised upon them by the accumulating blood and serum. These areas are at first protected against infection because of the excess of venous blood, which has a high restraining power upon germs.

HEMORRHAGE

By hemorrhage is meant the escape of the several constituents of the blood from the blood-vessels. It is said to be *arterial*, *venous*, or *capillary*, according to the vessel from which the flow of blood takes place, and *parenchymatous* when it comes from all of the vessels. Hemorrhage may occur either by diapedesis and extravasation through intact vessels (*hemorrhage per diapedesin*) or by actual rupture of a vessel (*hemorrhage per rhexin*). The former process is seen only in the capillaries and smaller veins; the latter occurs mainly in the arteries and veins.

Emigration and Diapedesis.—Under normal conditions a certain number of white corpuscles, by virtue of their ameboid movements,

escape from the capillaries, and become wandering cells which move about in the tissues or are carried by the lymph-stream. This process is called *emigration*. There is at the same time some transudation of plasma, which, with the leukocytes, enters the lymphatic circulation. Under certain abnormal conditions the red corpuscles also pass through the vessel wall and collect in the tissues. This is known as *diapedesis* (Fig. 3). It may be studied very readily under the microscope in the mesentery of a living frog. It is noticed that the red corpuscles approach certain parts of the wall of the capillary or vein and become fixed; then a small projection appears outside the vessel, opposite the corpuscle, and as this increases the corpuscle within grows smaller, until the whole body has gradually passed through. Not rarely several corpuscles pass

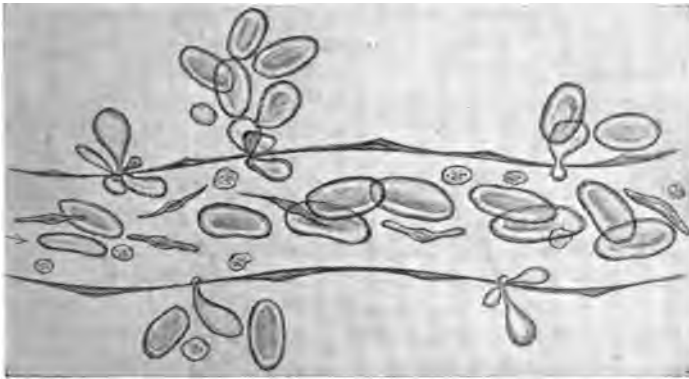


Fig. 3.—Diapedesis of the red blood-corpuscles through a capillary of a frog's tongue (after Thoma).

through in one mass, as has been particularly noted by Thoma. Outside the vessel the corpuscle at once assumes its ordinary shape.

Diapedesis was first studied by Stricker and Cohnheim. Arnold, whose investigations are most important, first believed that the emergence of the red corpuscles takes place through orifices or stomata; but later recognized, as is now generally believed, that the supposed stomata are merely accumulations of intercellular substance in certain places between adjoining endothelial cells or at the junction of several cells. The active cause of the extrusion of the red corpuscles is the pressure of the blood. It has been thought that chemical changes in the endothelial cells or the so-called stomata must precede the diapedesis.

The leukocytes emigrate from the vessel in exactly the same way as the red corpuscles, but mainly by their own ameboid movements. At the same time there is a more or less copious overflow of plasma.

Diapedesis is readily induced by mechanical compression of a vein, which elevates the blood-pressure; or it may follow elevation of blood-pressure from any other cause. On the other hand, with normal pressure increased permeability of the vessel walls may occasion diapedesis. Such degenerative conditions of the vessels may be due to the action of poisons, to various infectious diseases, to moderate trauma-

tism, or to temporary obstruction to the flow of blood into a certain area. Perhaps also altered states of the blood may play a part when both the vessels and pressure are normal. Hemorrhages by diapedesis are generally small and punctate (*petechiæ*), but may be quite large, as sometimes in the conjunctiva.

The solution of the endothelia or the intercellular cement substance may be caused by many toxins, and seems not to be dependent on any one chemical substance.

Multiple ecchymoses may result from obstruction of capillaries or small blood-vessels. Such obstructions occur in the form of hyaline thrombi in various infections, as a result of burns or freezing of the skin, as well as from exogenous and endogenous poisoning. Fat embolism and embolism of parenchymatous cells may bring about the same result.

Causes of Hemorrhage.—The ordinary form of hemorrhage *per rhexin* may be due to traumatism, to diseases of the vessels, to increase of the blood-pressure, and to certain vague nervous influences.

1. **Traumatic hemorrhage** may be due to direct laceration of a vessel or to contusions which merely weaken the vessel wall and lead to subsequent rupture.

2. **Diseases of the blood-vessels** causing hemorrhage generally originate from causes within the vessel, and are due to such conditions as poisoning, infections, cachexias, or the anemias. Among the diseases of the vessels are fatty degeneration of the intima or media, atheroma, and miliary aneurysm. On the other hand, the outer coat may be eroded by surrounding disease and hemorrhage ensues (hemorrhage *per diabrosin*). This is seen in phthisic cavities in the lungs.

3. **Increase of blood-pressure** may be absolute or relative. The former occurs from emotional excitement, from hypertrophy of the heart, during paroxysms of whooping-cough, croup, and various convulsive disorders. In asphyxia there is decided increase of blood-pressure both from vasomotor contraction and from the violent muscular efforts. Relative increase of pressure occurs when the pressure external to the vessel is reduced, as in balloon ascensions, or in the pleura in cases in which during violent inspiratory efforts the air cannot enter the lungs, as in the fetus attempting to breathe during labor.

4. **Neuropathic Hemorrhage.**—The nervous system exercises a peculiar influence upon the vessels. In cases of apoplexy, of epilepsy, and of section of the spinal cord and in other nervous conditions spontaneous hemorrhages from the nose or stomach, or into the lungs, suprarenal bodies, and other organs, are not infrequent. In the same group also are to be reckoned the instances of vicarious hemorrhage due to suppression of the menses and the remarkable cases of stigmatization. The last named is a condition in which under nervous exaltation or hysteria spontaneous hemorrhages occur from various parts of the body, especially from the parts wounded in the Crucifixion.

5. **The Hemorrhagic Diathesis.**—Certain persons present an inherited tendency to bleed spontaneously or after very trivial injuries. Such persons are known as "bleeders," and the condition as *hemophilia*.

The exact pathological condition which occasions the hemorrhages is still uncertain. Hemophilia is a familial disease manifested by extraordinary tendency to bleed either spontaneously or upon trivial injury. The hemorrhage may be external, submembranous, or interstitial. The diathesis is transmitted by the females and expressed by the males. The reverse has been known to occur. There is a lower coagulability of the blood, a prolongation of the clotting time, and probably a lowered tonicity of vessel walls. Rudolph and Cole cite two cases in which the clotting times were nine and one-half and nineteen minutes.

A hemorrhagic diathesis may also be developed as a result of various diseases, as typhus fever, anthrax, septicemia, or phosphorus-poisoning. The same is observed in the severe forms of anemia, like progressive pernicious anemia and leukemia. In these cases altered blood states and disease of the vessel walls are doubtless the causes at work.

Classification of Hemorrhages.—Hemorrhage may occur on free surfaces or into the tissues. In the former case various names are applied to designate the locality, such as *epistaxis*, nosebleed; *hemoptysis*, hemorrhage from the lungs; *hematemesis*, from the stomach; *enterorrhagia*, from the bowel; *metrorrhagia*, uterine hemorrhage between, and *menorrhagia*, at the menses.

Hemorrhages into the tissues take their names from the size and nature of the lesion. A hemorrhagic infiltration beneath a surface, as of the skin or mucous membrane, is called an *ecchymosis*, which if small and well defined is a *petechia*, but if large and diffuse, a *sugillation* or *suffusion*. A distinct accumulation of blood, constituting a veritable blood-tumor, is known as a *hematoma*. Infiltrations of a peculiar sort, involving localized portions of a tissue or organ, are known as *hemorrhagic infarcts* (*q. v.*).

Results of Hemorrhage.—A very large hemorrhage may cause sudden death by cerebral anemia. More frequently the patient remains collapsed for a time and then slowly recovers. The hemorrhage ceases spontaneously by the diminution in heart action, by clotting of the blood at the point of rupture, by retraction of the elastic vessels, and by pressure of the surrounding tissues. Blood extravasated in the tissues soon coagulates and subsequently undergoes disorganization, the red corpuscles breaking down into pigment matter, which may be carried away or deposited at the seat of hemorrhage. The fluid elements may be completely absorbed, or, stained with coloring-matter, may remain as a cyst in which cholesterol plates are usually found. The solution of a large blood collection is due to leukocytic enzymes and products of tissue cell destruction. A focus of hemorrhage may set up reactive inflammation and lead to encapsulation by new connective tissue. Sometimes hemorrhagic accumulations become inspissated and undergo calcification. Blood in the serous sacs does not readily coagulate, but mingles with the normal liquid secretion. It may be gradually absorbed or may undergo degenerative changes, especially when infected by micro-organisms. Large hemorrhages cause acute anemia; repeated small extrava-

sations may lead to profound secondary anemia. (These conditions will be more fully discussed under Diseases of the Blood.)

EMBOLISM

Embolism is the process in which foreign bodies of various kinds are carried in the blood and deposited in the smaller arteries or capillaries through which their size does not permit them to pass. The bodies deposited are called *emboli*.

Sources and Nature of Emboli.—The most common form of embolism is that in which portions of thrombi situated in the heart, the large veins of the extremities or pelvis, or on atheromatous patches in the aorta, are swept into the circulation and lodge in the smaller vessels. Softening of the original thrombus is generally the immediate cause. More rarely portions of a diseased heart-valve or of the intima of the heart or arteries, liver or placental cells, or parts of tumors are carried in the circulation and deposited as emboli. Embolism of large giant cells of the bone-marrow is common. Disorganization of the blood may cause embolism of pigment particles, as in malaria, or of small hyaline masses, as in burns and certain forms of poisoning. In cases of fracture of bones particles of fat may be dislodged from the marrow and enter the circulation, while in wounds of the large veins of the neck or elsewhere air-embolism is observed. Finally, masses of bacteria, scolices of echinococcus, and other parasites are serious forms of emboli.

Dust-embolism.—Small particles of coal, iron, marble, or clay entering the lungs in respiration sometimes penetrate the tissues, are largely taken up by phagocytic cells, and for the most part are carried to the bronchial lymphatic glands. If the latter are surcharged and soften, the dust particles may gain access to the circulation through the efferent lymph-channels of the gland or by rupture of the gland into neighboring veins. More rarely dust particles may enter the blood-vessels in the lungs directly by penetration. After their entrance into the blood they are deposited in the capillaries and substance of the liver, spleen, and bone-marrow, where they may remain permanently, either free or enclosed in fixed cells, or whence they may be removed by wandering cells. The final discharge occurs especially from the lungs, the tonsils, the lymphatic structures of the intestines, and from the liver in the bile.

Air-embolism.—Small quantities of air may occasion no serious disturbances; but when large quantities enter the veins the right heart is found full of frothy blood and the pulmonary arterioles are occluded by small bubbles. Sudden death in these cases is not unusual. Some experiments in dogs seem to cast doubt on the seriousness of air-embolism, but the matter is not yet settled. (See Caisson Disease.)

Fat-embolism.—Sudden death may occur when a large number of the pulmonary vessels are obstructed by embolic oil-drops. When the process is less extensive, little disturbance arises, as the oil is soon broken up into droplets and passes through the pulmonary capillaries, or it may be absorbed in the lungs.

Seats of Embolism.—The final place of lodgment of an embolus depends mainly on its source. Those derived from the general venous circulation are usually carried through the right heart to the lungs, where they occlude branches of the pulmonary artery. Emboli in the portal circulation may lodge in the liver, or pass through the liver to the heart and lungs.

Retrograde Embolism.—Sometimes portions of thrombi, tumor masses, other cellular emboli, or micro-organisms may be transported in the veins in a direction opposite to the normal blood-current. Thus emboli may be carried upward in the inferior vena cava and into the hepatic veins and so into the liver; or from any of the larger veins or even from the right heart backward toward the peripheral veins. This condition, known as retrograde embolism, is observed when some pulmonary disease, such as whooping-cough, emphysema, etc., causes increased intrathoracic pressure and consequently a positive instead of negative pressure in the large intrathoracic veins. There may be an actual retrograde current of blood, or the centrifugal transportation of the embolus may be more gradually accomplished by repeated impulses directed toward the periphery, each of which pushes it a little further.

Emboli coming from the left heart or from the aorta are distributed in the general arterial circulation. They are most frequently found in the spleen, kidneys, and brain. Other organs or the peripheral vessels may likewise be affected, but the results of embolism are less marked in them and are frequently overlooked. Emboli from the veins may reach the general circulation in cases in which the foramen ovale or septum ventriculorum is perforated (*paradoxical embolism*), or by being broken up into smaller emboli in the lungs and thus passing through the pulmonary capillaries. The latter is not infrequent in cases of fat-embolism of the lungs.

Results of Embolism.—A large embolus may cause sudden death by occluding one of the main branches of the pulmonary artery, one of the coronary arteries, or a large cerebral vessel. If the vessel is not wholly occluded, secondary thrombosis may complete the obstruction and death may be slow. In the case of less important vessels merely local anemia results. This may be relieved by establishment of collateral circulation, or may cause more or less extensive necrosis if not relieved. The original embolus and the secondary thrombus may undergo softening or organization in the same manner as ordinary thrombi (*q. v.*).

The results of occlusion of smaller vessels by emboli depend on the nature of the embolus. They are either purely *mechanical* when the embolus is aseptic, or *septic* when the embolus contains micro-organisms. The important mechanical result of small emboli is the pathological condition called *infarction*.

Metastasis.—The process of metastasis of tumors and of infectious diseases is closely allied to that of ordinary embolism, and should be considered as that form of embolism in which there arises at the point of settlement a condition similar to that at its origin. Small particles of tumors in the one case, or of infected thrombi or tissue in the other, enter the blood-vessels or the lymphatic channels and are carried to neighboring or distant parts of the body, where they lodge in capillary vessels. In the case of tumor-embolism the embolus may grow and occasion a metastatic nodule; in case of infectious processes secondary foci of the infectious disease result.

INFARCTION

Infarcts occur in situations in which there are small arteries having only capillary or, at most, very slight arterial anastomosis with neighboring arteries. Such arteries were called *end-arteries* by Cohnheim. They are found especially in the kidney, spleen, lungs, retina, base of

the brain, and parts of the heart. When one of these is occluded by an embolus infarction may occur.

Infarcts are situated in the peripheral part of the organ, and are harder than the surrounding tissue. They are wedge shaped, the base being outward toward the periphery of the organ. Infarcts may sometimes result from occlusion of a number of adjoining arterioles or capillaries, and in this case are irregular in outline. There are two forms of infarction, the red or hemorrhagic, and the white or anemic. The former are dark red in color, and have the appearance of wedge-shaped areas of hemorrhage with coagulation. Anemic or white infarcts present the same general features, but are less elevated and are yellowish or grayish in color. They are frequently surrounded by a zone of congestion or hemorrhage (Fig. 4).



Fig. 4.—Old anemic infarct of spleen.

Formation of Infarcts.—The first effect of occlusion of an end-artery by an embolus is stoppage of the circulation beyond the embolus. A wedge-shaped anemic area results. This may remain anemic and undergo coagulation necrosis, with the formation of an *anemic* or *white infarct*. In other cases, however, the vessels of the occluded area, after a temporary period of anemia, become overfilled with blood, extravasation occurs, and a *hemorrhagic infarct* results. Various theories are offered to explain the persistence of anemia in the first case and the overfilling with blood in the second. In anemic infarcts the persistent anemia in some cases is due to thrombosis in the venules which receive the blood from the occluded end-artery and in the anastomotic capillaries. At times rapid swelling of the parenchymatous cells of the organ compresses the capillaries and maintains the anemia. Some contend that white infarcts are frequently formed by rapid absorption and removal of the coloring-matter of the blood from hemorrhagic infarcts. In the latter the overfilling of the vessels results either from a back

flow of blood from the veins (Cohnheim) or from free capillary anastomosis. The latter would be especially apt to occur when the general or local blood-pressure was previously elevated, or when the lodgment of the embolus caused reflex contraction of the surrounding vessels, and thus overflow of blood into the occluded area through the capillary anastomoses. The hyperemia thus produced soon leads to extravasation of blood, because the vessels of the occluded areas rapidly undergo degenerative changes. The continuance of the dark color in the hemorrhagic infarct is due to deposition of iron-bearing pigment derived from hemolysis by autolytic or tissue enzymes. Infarcts in the lungs are nearly always hemorrhagic; those in the kidneys and especially the spleen are frequently anemic. In the brain irregularly shaped areas of anemic necrosis (softening) are the usual result.

Subsequent Changes.—In anemic infarcts coagulation necrosis and caseation are the marked degenerative changes. The broken-down tissue is gradually absorbed and reactive inflammation and organization cause cicatrization. Not infrequently a small amount of calcareous matter is deposited, especially in infarcts of the lungs. In hemorrhagic infarcts the extravasated blood breaks up into pigment matter and the tissues suffer degenerations similar to those seen in anemic infarcts. The final result in either case is generally a scar, which is pigmented in cases of hemorrhagic infarcts. More rarely infarcts undergo liquefaction and cyst formation, especially in the brain. The infarct may become infected by micro-organisms after its formation and abscess may result, as in cases in which the embolus itself was an infectious one.

Infectious embolism occurs in cases of purulent softening of thrombi, in cases of local suppuration or necrosis, in ulcerative endocarditis, and the like. The first effect may be the formation of a hemorrhagic or anemic infarct; but the micro-organisms soon multiply and invade the tissues, causing suppurative or gangrenous processes. Metastatic abscesses are produced in this manner. Similar results follow when an infarct is secondarily infected. This is not infrequent in the lungs, where the air-passages furnish a ready path for the entrance of micro-organisms.

Pulmonary infarcts may be due to embolic occlusion of the blood-vessels, but also to obstruction of a bronchiole. Any kind of hemorrhagic extravasation in the lungs may assume a wedge shape, because the area infiltrated is the wedge-shaped area included in the divisions of a terminal bronchiole. (For details, see the chapter on the Lungs.)

THROMBOSIS

Thrombosis is the coagulation of blood within the blood-vessels or heart during life. At the very beginning of the process the formation is not a coagulum in the ordinary sense, but subsequently coagulation is the essential feature. After death clots form within the heart and vessels, as in blood removed from the body.

Causes.—The conditions favorable to thrombosis are alterations in the blood-current, changes in the vessel walls, and alterations in the

blood itself. For the most part two or all of these conditions are present in cases of thrombosis.

Alterations in the Blood-current.—Anything which slows the current, such as narrowing of the blood-vessels, weakness of the heart, or pressure upon the vessels, favors thrombosis. Complete arrest of the current in a part may lead to ordinary clotting, such as occurs postmortem; but with careful precautions a vessel may be ligated at two points without the occurrence of clotting in the occluded portion—at least for a long time. Some change in the blood-vessel wall is generally necessary in addition. Some sudden change in blood-pressure or rate of flow, some back pressure or blood eddy may permit the settling upon the intima of sufficient blood-platelets to start a clot. Thrombi due to slowing of the current are frequently seen in the heart, the vessels of the lower extremities, and in the sinuses of the brain in the course of exhausting fevers or other asthenic conditions. They are called *marantic thrombi*. In many of the latter micro-organisms have important etiological relations.

Changes in the vessel walls play an important part. Atheroma, inflammatory or degenerative changes in the vessels of areas of inflammation or necrosis, ligation and other traumatic injuries, and diseases of the endocardium are all examples of conditions leading to thrombosis. In many cases of thrombosis apparently due to slowing of the current of blood micro-organisms have been the more important factors by causing primary infective lesions of the endothelium. Dilatation of the arteries (aneurysm) or veins (phlebectasia) or of the cavities of the heart acts largely by slowing the current of blood or by producing irregular currents.

Alterations in the Blood.—It is believed by Aschoff that some alteration in the blood itself is necessary, and that without this, changes in the vessel wall are insufficient. These blood alterations may consist of clumping of platelets, collections of hemolyzed red blood-cells, and the like.

Experimentally, thrombosis may be induced by injection into the circulation of extracts of the thymus gland, the suprarenal bodies, the testicles, and other organs. These extracts contain large quantities of the fibrin-ferment regarded by Schmidt as an essential factor in coagulation. Pathologically, it is probable that the tendency to thrombosis in typhoid fever, sepsis, and other diseases is due to increase of similar fibrin-forming factors in the blood. The name *ferment thrombosis* is applied in these cases.

The presence of bacteria in the blood in cases of thrombosis and within the thrombi themselves indicates a probable relationship of great importance. Some bacteria (especially staphylococci) seem particularly potent, while others apparently have little effect. The mode of action of the bacteria has not been fully established, but hemolytic activity and injurious effects on the lining of the blood-vessels may now be considered sufficient to explain thrombosis, on the basis of a reduction of the anticoagulating power of endothelium. Bacteria seem able to induce hyperinosis, or an increase in the fibrin-forming elements.

Hemolytic action is also the probable explanation of the frequent thrombosis met with in various mineral poisonings and in auto-intoxication such as follows freezing or burns.

According to present-day views, coagulation of the blood is the result of a special form of gelatinous precipitation of *fibrinogen*, a normal constituent of the blood-plasma under the influence of *fibrin-ferment* or *thrombin*. The latter is probably not a true ferment in its mode of action, but seems rather to enter into a physical or physicochemical combination with the fibrinogen. Thrombin is a derivative of various cells of the body, especially the leukocytes and vascular endothelia. It occurs in the cells as *prothrombin*, which requires for its activation or conversion into thrombin, calcium salts and probably also certain so-called thromboplastic substances derived from tissues. In the blood within normal blood-vessels coagulation is prevented by the action of antithrombin (Howell). According to the views here expressed the process of coagulation may be tabulated as follows:

Cells → thromboplastic substance. Thromboplastic substance + calcium + prothrombin = thrombin. Thrombin + fibrinogen = fibrin.

Pathological Anatomy.—The appearance and the construction of thrombi depend upon the manner of formation.

When formed in consequence of almost complete stoppage of the circulation they are dark-colored, soft, *red clots*, similar in every way to postmortem coagula; and under the microscope show fibrillar fibrin enclosing mainly red corpuscles.

Yellowish or white thrombi are formed slowly from actively circulating blood and are more consistent. Their composition will be understood from the mode of formation. In the normal circulation the red corpuscles move in a column in the center of the stream, separated from the wall of the vessel by a plasmatic zone in which the leukocytes may be seen. When the circulation is slowed, plaques approach the vessel wall, and tend to adhere in small masses to any point of disease in the endothelium and also to each other. This has been termed *conglutination* of the blood-plaques.

In the ordinary thrombus, after primary conglutination of the plaques, leukocytes are added, and red corpuscles in great or small numbers, according to the manner of formation of the clot, whether rapid or slow. White thrombi consist of conglutinated plaques, leukocytes, and fibrin. They first appear as hyaline, viscid masses, but subsequently become granular from partial disintegration. If the circulation is alternately slow and more rapid, distinct layers are seen in the thrombus, first dark colored from admixture of red corpuscles, then lighter in hue. Such thrombi are called *stratified*. If the circulation is irregular from dilatation of the vessels or from other causes, the light and dark areas of the thrombus may be more irregularly disposed.

The thrombus first formed is the *primary thrombus*. Subsequently it extends by additions (*secondary thrombus*) in the direction of the current of blood as far as the next collateral branch of the vein or artery, into which the thrombus frequently extends as a rounded prominence. In the case of the veins a new thrombus may start from such projection (Fig. 5), and eventually the clot may in rare cases extend as

far as the heart (Fig. 6). The thrombus may be *lateral*—that is, when it lies against the vessel wall—or *obstructive*, when the lumen is completely obliterated. In the veins small thrombi are frequently formed in the valvular pouches in marantic subjects. In the heart thrombi are especially common on diseased valves, in the auricular appendages, and in



Fig. 5.—Thrombus in the femoral vein in a case of phlebitis (from a specimen in the Museum of the Philadelphia Hospital).

the intertrabecular spaces. They frequently appear as polypoid masses, and may be attached by slender pedicles. A curious form, called *ball thrombi*, is seen in the auricles. These are rounded clots wholly or almost wholly separated from the wall, and may occasion serious obstruction



Fig. 6.—Cystic thrombi of heart chamber.

at the orifices of the heart. The internal softening is probably due to leukocytic enzymes acting in the center, protected there from the anti-enzyme of the blood.

Effects.—Frequently the collateral circulation is so quickly established that no untoward results are seen. When a large vein is ob-

structed, venous congestion and dropsy may follow; obstruction of an artery causes local anemia, and subsequently, if the collateral circulation is not established, degenerations or necrosis. Thrombotic obstruction of small arteries may cause hemorrhagic infarction. Embolism and, if the thrombus is infected, general pyemia may result from softening of the thrombus.

Subsequent Changes.—After their formation all thrombi contract. In this way the red forms may become light colored by extrusion of the red corpuscles, or by hemolysis if bacteria or toxins are responsible for the thrombosis. In small vessels red thrombi often become light colored by removal of hemoglobin and a species of hyalin transformation. These may have the appearances of white thrombi and are only distinguished by careful examination.

After the thrombus has contracted it may undergo various degenerative changes. Frequently the white corpuscles, plaques, and



Fig. 7.—Thrombosis in cardiac chambers, showing cyst-like structure (Orth).

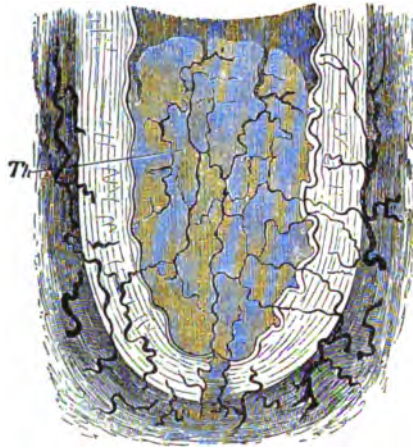


Fig. 8.—Branch of the brachial artery after amputation, showing vascularization of the thrombus, Th (Weber).

fibrin are broken down into an emulsion by liquefaction necrosis and fatty degeneration, and the red corpuscles converted into granular pigmented masses. These softened portions are swept into the circulation and occasion embolism. Frequently this form of *simple softening* occurs in the center of large thrombi and gives rise to cyst-like formations (Fig. 7).

A more serious form of softening occurs when the thrombus is infected by micro-organisms. In this case true *purulent softening* takes place, and the wall of the blood-vessel shares largely in the suppurative processes. This form occurs especially in the thrombi blocking blood-vessels of suppurating or necrotic tissues. General pyemia and infectious embolism result.

A more favorable termination of a thrombus is *calcification*. This

is most frequent in the clots in dilated veins, the calcareous thrombi being known as *phleboliths*. *Arterioliths* and *cardioliths* are rarely met with.

Organization of the thrombus may result from the irritation it occasions. New blood-vessels and proliferating connective-tissue cells spring from the vasa vasorum and lining membrane of the blood-vessel as well as from endothelial cells covering the thrombus, and penetrate the thrombus (Fig. 8). From these organization proceeds as elsewhere, and as it advances the thrombus itself is absorbed. Finally, the clot is fully replaced by connective tissue enclosing a small amount of blood-pigment or calcified remains of the thrombus. The blood-vessel may be converted into a solid fibrous cord, or may be distorted and narrowed by bands of connective tissue in the interior. Sometimes after partial vascularization of a thrombus small vessels running parallel with the lumen of the obstructed vessel become dilated and thus partly reestablish

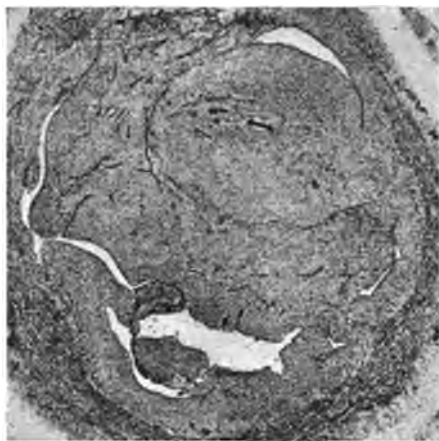


Fig. 9.—Canalization of a thrombus (Karg and Schmorl).

the channel. This is termed *canalization* of the thrombus (Fig. 9). In other cases canalization may begin as a process of simple softening.

The clotting of blood within body cavities, in extravasations, or upon wounds is favored by the presence of tissue coagulins and bacteria in addition to the leukocytes and platelets. Hyaline thrombi seen in small vessels and free in organs are due to an agglutination of erythrocytes or platelets by bacterial or other toxins. They are probably free of fibrin, although staining like it.

EDEMA

Definition.—The term “edema” is applied to a condition in which the liquid within the tissues is increased in quantity.

Etiology.—It is primarily necessary to understand the methods by which the liquids normally present in the tissues escape from the blood-vessels, their original source.

Several processes are concerned in this escape of fluid. In the first place, the pressure of the blood serves to cause a certain amount of *direct filtration*, just as liquid enclosed in tubes of permeable animal membrane escapes when the pressure outside is less than within. In this process of direct filtration the state of the tissues themselves plays a part. If the normal elasticity of the tissues and degree of pressure of the liquid in the interstitial spaces are lowered, liquid escapes through the capillary walls to equalize the pressure. A second process at work is that known as *diffusion* or *osmosis*. In this there is an exchange between the blood and the tissue liquids, certain substances being taken into the blood in exchange for water and other constituents of the blood-plasma. The liquid thus discharged from the blood-vessels enters into the metabolic activity of the tissues to a greater or less degree, is somewhat altered in character, and the surplus is carried off in the lymphatic capillaries as *lymph*. Certain physiologists (Heidenhain *et al.*) believe that there is a further and very important factor of a vital sort. This is described as an active secretory function of the endothelial cells of the capillaries and lymphatic spaces; so that, according to this view, lymph formation is in a measure at least a direct secretion. This view, though not generally accepted, is supported by many facts. Meltzer suggests that endothelium acts as a carrier of lymph and solid particles from the blood to the tissues.

Briefly, then, lymph formation may be described as the escape of water and other substances through a more or less permeable membrane, the capillary walls, in consequence of direct filtration, osmosis, and probably secretion. The quantity present in the tissues depends upon the quantity escaping from the blood-vessels and the amount carried away by the lymphatic circulation.

The causes of increased accumulation of liquid in the tissues may then be readily determined. Among these are: (a) increase of blood-pressure, or (b) decrease of tissue elasticity and pressure; (c) alterations of the blood rendering it more diffusible, or (d) of the liquids in the tissues increasing the osmotic power of these; (e) increased permeability of the walls of the blood-vessels; (f) obstruction to the flow in the lymphatic vessels. These causes will be considered separately with reference to certain well-known clinical types of edema.

(a) **Increased blood-pressure** always occasions increased escape of liquid from the vessels (transudation) and thus increased formation of lymph. In active hyperemia with excess of pressure the amount of liquid rarely becomes so great that the lymphatic vessels cannot carry it off, and edema does not, therefore, occur. In passive congestions, however, as in heart disease, pressure upon veins, etc., the escape of liquid becomes more rapid and copious, and the lymphatic circulation is insufficient. Edema or dropsy results. In this process of direct filtration the transudate consists mainly of the water and saline constituents of the plasma and to a relatively small degree of the albuminous constituents.

(b) **Decreased tissue elasticity and pressure** are rarely factors of prime importance, though they may be contributing causes in many cases. In one class of cases termed "oedema ex vacuo" they are the

principal causes. In these cases liquid escapes from the blood-vessels to fill a space left vacant by disease or atrophy of tissue elements. This is frequently seen in the subarachnoid spaces of the brain and in other parts of the central nervous system.

(c) **Alterations of the blood**, though theoretically very important as direct causes, probably act indirectly. It has been found by experiment that artificial hydremia, even though combined with considerable increase of the bulk of blood, does not cause edema unless by some means the walls of the blood-vessels have been injured. It is probable, therefore, that the edema of anemic and marantic persons is similarly due to increased permeability of the vessels. This in itself might occasion edema, though the degree is probably greater as a consequence of the anemic state of the blood. The vascular disease itself is probably in some way (perhaps by the action of circulating toxic substances) brought about by the condition of the blood.

(d) **Increased permeability of the capillary walls** is of great importance and probably plays a part in every case of edema. Experimentally it is easy to prove that this factor alone may cause pathological transudation. Applications of heat to a part or the introduction of poisons capable of causing disease of the walls of the blood-vessels may thus occasion edema. Clinically this factor is of importance in the edema of Bright's disease. Formerly the dropsies of renal disease were attributed to hydremia, but the experiments cited above show this factor to be insufficient. On the other hand, changes of the vascular system are known to occur in Bright's disease, and particularly in cases usually attended with marked edema (glomerulonephritis). Changes in the blood may, of course, contribute, as may also stasis due to cardiac weakness.

Disease of the capillary walls is also an important cause of edema in and about areas of inflammation (inflammatory edema). In these cases the toxic causes and products of inflammation doubtless attack the walls of the vessels and render them more porous. Such edema may occur only in the vicinity of an inflamed area, or may be widespread. Thus in some cases edema of the lungs and other internal organs may be occasioned by bacterial toxins derived from a distant focus of infection.

Cases of hereditary edema have been described. These may owe their origin to a congenital excess of vascular permeability.

Finally, there are cases of edema in which the nervous system seems to exercise an influence. Among these are the dropsies attending cases of neuritis, neuralgia, or organic diseases of the cord. In these instances changes in the blood-vessels and perhaps in the tissue elasticity may be important causes. An interesting form of this sort is that known as *angioneurotic edema*, in which local edema of various forms (often as giant urticaria) makes its appearance under the influence of nervous irritations.

(e) **Obstruction of the lymphatic circulation** does not ordinarily occasion edema because the collateral circulation is sufficient to carry away the lymph. When, however, a larger trunk, especially the thoracic

duct, or numerous smaller lymphatics are obstructed edema may result. This is observed in the chylous ascites due to obstructions of the thoracic duct and in the edema of elephantiasis.

(f) **Alterations of the liquids of the tissues** may, conceivably, occasion increased diffusion of liquid, but practically little is known of the operation of this element.

While the escape of fluid from vessels to tissues may be explained under the preceding headings, other factors must account for its remaining outside lymph- and blood-vessels. This has been explained by the statement that dropsical tissues and fluids contain an excess of sodium chlorid. This is not always the case. Fischer claims that in parts subject to edema there is increase in acids, in the presence of which colloids are altered so that they take up and hold more water. The acids accumulate as a result of overproduction through improper oxidation or because of abnormal retention.

Pathological Anatomy.—Edema may take various forms, according to its situation. In some cases it is localized, affecting a limited part of the body, as a single organ or member. In other cases it is widespread in the subcutaneous tissues and skin, when the term “anasarca” is applied. It may occur in the serous cavities in the form of serous transudates (hydrothorax, ascites, hydropericardium, etc.).

The liquid itself varies in character according to the cause. In the pure transudates due to increased filtration the liquid is watery, low in specific gravity (below 1016), and comparatively poor in blood-corpuscles and albuminous constituents. In cases in which disease of the vessel walls has played a large part in the causation, especially in the inflammatory edemas, the liquid is more dense and contains more corpuscles and albuminous bodies.

The transudate first occupies the lymph-spaces or interstices of the tissues, causing a more or less uniform swelling and boggiess. The tissue pits on pressure, and on section more or less abundant liquid exudes. The solid organs (kidneys, liver) are lighter in color, less dense, and more moist on section than normal; but the appearances of edema are here less characteristic than in the subcutaneous or submucous tissues, or in the softer organs like the lungs and brain.

Microscopically, the tissue elements are seen to be pushed apart by the transudate, and in some cases the cells themselves may be diseased. (See Dropsical Infiltration.)

Results of Edema.—The function of edematous parts is necessarily impaired. Sometimes serious consequences ensue, as in the case of edema of the epiglottis, the lungs, or the brain. Secondary changes may occur in parts the seat of continued edema. Among these are various degenerations of the cells and a productive change in the connective tissues. The latter is well illustrated in the sclerotic change in the subcutaneous tissues of long-standing dropsy, elephantiasis, etc.

CHAPTER IV

RETROGRESSIVE PROCESSES

ATROPHY

Definition.—Atrophy is a condition in which a tissue or organ undergoes a more or less uniform diminution without definite disease of its constituent parts. It is extremely difficult to draw a sharp line between atrophy and degeneration. Frequently one of these conditions merges into the other.

Hypoplasia.—This term is applied to a condition in which certain organs or tissues fail of their normal development. Thus the heart and blood-vessels and the internal genitalia have been found incompletely developed in some cases of chlorosis; and similar conditions have been found in other diseases or apart from manifest disease. It is difficult to determine in some cases whether the lack of development is purely the result of deficiency in the developmental processes or the result of congenital disease. Thus, in the state called *infantilism*, in which the body as a whole remains undeveloped, there is sometimes a relationship with cretinism or other diseases of glands of internal secretion, and primary disordered action or deficiency of the thyroid gland, hypophysis, etc., is the underlying cause. Occasionally an organ or part of the body is entirely wanting. To this condition the name *aplasia* is given.

Etiology.—The causes of atrophy may be varied. It occurs as a result of want of functional demand, as in the atrophies affecting palsied limbs; and sometimes as a result of disturbances of the trophic nervous system, as in diseases of the anterior horns of the spinal gray matter. In the latter instances lack of use is a contributing cause. In the involution processes of old age there is more or less general atrophy, which might be designated as physiological. Similar normal or physiological atrophy occurs in certain organs before the general manifestations of old age. Thus, the atrophy of the thymus gland in early childhood and of the genital organs at the menopause are instances of cessation of function, and consequent or concomitant atrophy of physiological character. Atrophy may be more definitely pathological and the result of distinct causes, such as want of local or general nourishment by occlusion of the vessels, pressure, etc. In these cases the process may be purely atrophic, or there may be distinct degenerative disease of the cells with diminution of bulk.

Pathological Anatomy.—Atrophy may be *simple* or *numerical*. In the former kind, to which the term “true atrophy” might also be applied, the individual cells decrease in size without manifest disease; in the latter the cells are reduced in number, and are usually first altered by some form of degenerative disease, so that the process is not, strictly speaking,

true atrophy. The parenchyma of organs suffers first and most characteristically, the connective tissues remaining unaffected or even undergoing hyperplasia. In true atrophy the cells may present no definite alteration, excepting perhaps slightly increased pigmentation. This is sometimes due to the fact that the normal pigment does not suffer reduction as do the other constituents of the cell, but in other cases there is actual deposition of pigment (hematogenous). Cases of the latter kind are designated as *brown atrophy* (Fig. 10). This is seen most strikingly in the heart muscle in advanced old age or in persons dead of some chronic cachectic disease. In some of the conditions generally described as atrophy the cells show degenerations of various forms, such as cloudy swelling, coagulation necrosis, fatty degeneration with vacuolization, and other gross alterations of structure.

Secondary degenerative changes may occur in the connective tissues after the parenchyma cells have become atrophic. Thus, after the physiological atrophy of the thymus gland has occurred the connective tissues of the gland and of the surrounding parts become converted into fatty tissue. In other cases myxomatous change may be observed. Such a fatty or myxomatous change may give rise to pseudohypertrophy.

Organs which have undergone atrophy are often quite irregular on the surface from unequal involvement of the different constituents. The consistency may be little changed or may be greatly reduced, particularly when some form of cellular degeneration is present. On the other hand, the organ may be hard and tough from secondary hyperplasia of the connective tissue. The capsule is generally wrinkled from the shrinkage of its contents, and secondary thickening is not unusual, especially in the heart and spleen. The color of the organ, like that of the individual cells, often becomes darker than normal, and may be decidedly changed in brown atrophy.

In cases of pressure-atrophy various distortions of the affected organ may be observed. These are particularly marked in the livers of women who have laced excessively. The right lobe of the organ often presents a deep groove or furrow corresponding with the lower border of the ribs, and each of the ribs with which the organ comes in contact may cause a depression.

Pathological Physiology.—The function of an atrophic organ is necessarily impaired. In the atrophies of old age this may be of little consequence, as the functional demand grows less and less. In premature atrophies general as well as local disturbances may occur. These disturbances vary with the varying functions of the organs, and will be separately discussed.



Fig. 10.—Brown atrophy of the heart muscle.

THE SO-CALLED INFILTRATIONS AND DEGENERATIONS

There are certain pathological processes of a retrogressive character to which the names "infiltration" and "degeneration" have been given. Data are growing to show that several of these may be but stages of cell necrosis, and that a sharp distinction is not possible between infiltration and degeneration. In order not to confuse the reader the subjects will be taken up under their customary names and an attempt will be made to show their relationships.

CLOUDY SWELLING

Definition.—Cloudy swelling, also termed "albuminous infiltration" and "parenchymatous degeneration," may be defined as an edema of the cellular protoplasm, with granular alteration in the protoplasmic protein and the production of opacity.

Etiology.—Cloudy swelling is an almost universal accompaniment of inflammations. Circulatory disturbances (anemia) were formerly supposed to be important, but are now considered to be of little significance. Fever *per se* can produce cloudy swelling, probably not so much the result of the simple degree of heat as of metabolic disturbances induced thereby. The most frequent cause of cloudy swelling is intoxication, either by bacterial toxins, as in the various infectious conditions, or by innumerable organic and inorganic substances. Cloudy swelling is also caused by nutritional disturbances; starvation of an organ will produce it, as the first stage of atrophy; and, on the contrary, the cells may in other cases be so overloaded with nutritional substances as to become temporarily transformed into this condition, as in the glandular epithelium of the liver during active digestion. It is further known that excessive cellular activity may result in a cloudiness of the protoplasm, as in the kidney and in glands excited by nervous stimulation. These latter processes should be viewed as normal phenomena analogous to the physiological fatty degenerations.

Pathological Anatomy.—The swollen cells present a fine opacity which under high powers is seen to be due to the presence of diffuse refractile granules (Fig. 11). The normal protoplasmic granulations (Altmann's granules) may partly or wholly disappear; in muscle-fibers the striations are obscured or obliterated. Vacuolation may be seen in the late stages. The cell wall becomes indistinct, so that the cells appear to have coalesced. The nuclei may be little altered, but are commonly obscured by the degeneration. The nuclei are somewhat more deeply stained at first, but shortly undergo some chromatolysis, becoming indistinct when their sharpness is destroyed by both the smaller cytoplasm and their own degeneration. Generally the chromatin becomes diffusely stained; it may elect the acid stains or may refuse all staining. In late stages the entire cell may lose its normal reactions to staining reagents. The distinctive granules are not soluble in alcohol or ether, but are dissolved by acetic acid and alkalis. Cloudy swelling may be the forerunner of, or at least go over into, fatty degeneration.

The large glandular organs, the liver and kidneys, illustrate the condition exquisitely. The entire organ is symmetrically swollen; the general consistency perhaps a little decreased. On section, the surface may be found a little moist and the parenchyma protrudes. The tissue presents an opaque pallor, suggesting the appearance of boiled flesh.

Seats.—The glandular epithelia (liver and kidney) and the muscle-fibers are the striking seats of this degeneration.

Pathological Physiology.—The opacity seems to be due to a coagulation or precipitation of a part or all of the protoplasmic protein. Some systematic writers have attempted to divide it into two groups: albuminous infiltration, in which the material has been deposited in the cell and then been precipitated; and albuminous degeneration, in which the inherent cellular protein has been precipitated. It is doubtful whether this division is justified. The chemical relations are entirely obscure. It is as yet incomprehensible how bacterial toxins, them-

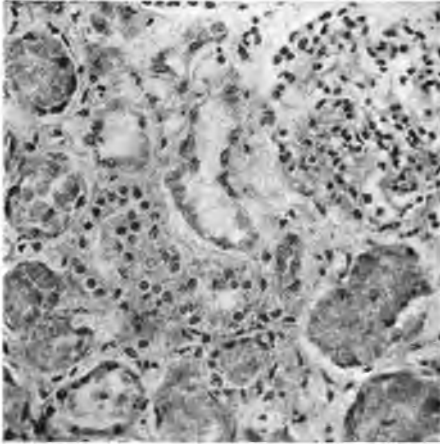


Fig. 11.—Cloudy swelling and necrosis of the epithelial cells of the renal tubules, due to sublimate-poisoning (Karg and Schmorl).

selves apparently proteins, can precipitate other and higher proteins. In the case of inorganic poisoning (metallic salts, acids) the process is more readily understood. The swelling of the cell is probably a simple edema, due, it may be inferred, to disturbed osmotic relations. This has been termed "granular disintegration," and may be considered as a stage midway between cloudy swelling and dropsical degeneration (*q. v.*).

Bell has lately shown that fatty and dropsical conditions of the organs give the gross appearance of cloudy swelling, and that all such degenerations need not be of the same microscopical appearance. He thus believes that the gross diagnosis "cloudy swelling" covers several states, and even the minute picture does not indicate an entity.

The function of organs is more or less disturbed by this form of degeneration. Complete recovery is easy and frequent. If, however, the causes persist, the cells pass into other degenerations, usually fatty metamorphosis.

FATTY INFILTRATION

Definition.—Fatty infiltration is the deposition of fats derived from the circulation in cells and tissues which normally contain none, or the deposition of an excess of fats in cells and tissues in which it normally occurs.

Etiology.—Fatty infiltration may be physiological or pathological. In conditions of general obesity the regular consumption of excessive quantities of nourishment may lead to the most marked degrees of fatty infiltration; an inherited predisposition and lack of exercise act as contributing causes. In rare instances it seems possible that with the normal physiological diet persons of exceptional digestive power and living under conditions which restrict combustion may become affected with pathological fatty infiltration. The condition may occur during pregnancy, and is frequent at the menopause. In a large class of cases an abnormal diet, or the presence in the diet of substances which aid in

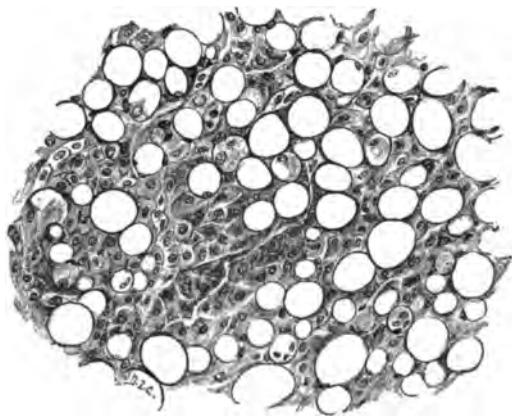


Fig. 12.—Fatty infiltration of the liver.

the formation of fats, such as alcohol, are responsible for the condition. It is doubtful whether poisons produce general fatty infiltration; they frequently, however, indirectly produce local or visceral infiltrations. Arsenic and antimony are examples. In cachexias certain organs may become loaded with fats, as is sometimes seen in the liver in phthisis. In carcinoma the cells of the neoplasm may become infiltrated with fats. In organic diseases of the nervous system accompanied by extensive disintegration of myelin, in bone diseases, and even following fractures or of operations on bones, the liberated fats are taken up by the circulation and deposited in susceptible localities. There is a rare form probably entirely of senile origin, and also a type which appears at puberty. Of general diseases that may cause general fatty infiltration, chlorosis and diabetes may be mentioned. Fats may be deposited locally as substitution tissue, as in the capsule about sclerosed kidneys, in the place of atrophied muscular fibers, in the bones, and about areas of

local disease. The protective areas of fibrous tissue which wall off pathological processes of various kinds may become extensively infiltrated.

Pathological Anatomy.—The fat may be diffuse, in localized areas, or in streaks along the planes of fibrous tissue. The appearances naturally vary with the tissue affected. The connective tissue rather than the parenchyma usually displays the disease. The microscopical picture in connective tissues is precisely the same as that of normal adipose tissue. The deposits in *connective tissue* are most prominent in *various fasciæ* and along the fibrous strands, *under the endothelial membranes*, about the lymph-channels, *between the muscular fibrillæ*, and to a marked extent just beneath the true skin. In the kidney the collections are *between the tubules*; in the liver, in the fibrous trabeculæ, but *especially in the hepatic cells*; in the heart, underneath the serosa and between the bundles of fibers. Within the parenchyma cells, and this is most marked in glandular epithelial cells, the fat is seen as distinct drops within the cell wall. The fat-drops are always of considerable size, and soon run together, forming one drop, which pushes the protoplasm and nucleus against the cell wall, giving the so-called seal-ring appearance. The nuclei, though flattened, are usually normally distinct, show a nucleolus, and stain well; the cell protoplasm is clear and presents its normal granules; the cell wall is intact, though often bulging to accommodate the excess of contents. In rare, prolonged, and extreme instances the bulk of the fat may be such as to interfere with the functions and nutrition of the cells, whose nuclei and protoplasm will then show pathological alterations. Crystalline formations, as of margarin and cholesterolin, and tiny balls of lecithin may be present, but are more often seen in fatty degenerations. The fat may be stained with osmic acid or sudan III.

Seats.—The favorite seats of fatty infiltration are the subcutaneous and subserous tissues, the mesenteries and omentum, along the fasciæ, between the muscles, about the kidneys, and in the liver and heart. The lungs and central nervous organs are rarely and only slightly affected.

Pathological Physiology.—The above description is intended to define this condition rigidly as an infiltration of fat into otherwise normal cells or tissues, distinct from any possible formation of fat in them. Infiltration arises whenever there is an abnormal quantity of fat in the circulation; the causes of this were pointed out in the etiology. Infiltration into imperfect or diseased cells may, however, occur with only normal quantities of circulating fat. All cells and tissues are not of the same degree of susceptibility; when, therefore, isolated areas occur in unusual localities a pre-existing disease should be suspected.

The assumption of fat and its retention in the form of globules must be referred to an inadequacy of the oxidative powers of the cell. This same is true for fatty degeneration, but here we may have added a destruction of the natural fat combination in the cell. Here also the absorbed fat remains in small globules or granules.

Unless very extreme, fatty infiltration does not seriously embarrass the functions nor threaten the existence of tissues, and complete recovery and restitution are the rule. It may, however, cause mechanical embarrassment or may lead to secondary degenerations, which, particularly in the heart, may be of serious consequence to the organ.

FATTY DEGENERATION

Definition.—This was formerly defined as a metamorphosis, the conversion of the cellular protoplasm into fat. The classical physiological illustration is the fat production in the secretion of milk. Here the nature of this process has not, however, been determined. The majority of the secreting cells neither die nor show pathological alterations; while in the case of such as are cast off, as colostrum cells, it has not been shown that their fat was not an infiltration.

Etiology.—Fatty degenerations frequently follow upon cloudy swelling, and the causes detailed for the one apply also to the other. Of all agents, poisons are the most important. These may be metallic, as mercury, arsenic, lead, phosphorus—indeed, most of the metals. Compounds which directly bind the hemoglobin or reduce it, or break up the red corpuscles, likewise produce it; such are carbonic oxid, chlorates, pyrogallie acid, some coal-tar compounds, etc. Certain poisons, like chloroform, ether, iodoform, and the acids, seem to act directly on the cell nutrition. In the case of most of these substances it seems to have been shown in more or less accurate chemical studies that the poison acts by disturbance of the cellular metabolism. The toxins of bacteria are causes of importance, but their mode of action is not clear, and the analogy with the metallic poisons which naturally suggests itself has not been made out. In anemias and cachexias fatty degeneration is common; it is rare in uncomplicated chlorosis. The degeneration in these cases was formerly regarded as due to suboxidation. Since, however, it has been shown that no suboxidation occurs in such chronic anemias, the degeneration may best be classed as toxic. It seems possible, however, that extreme hemorrhage can produce fatty degeneration by suboxidation. Metabolic diseases can also produce it, as is sometimes seen in diabetes. Fever can produce it, but the temperature must be high and prolonged.

Local fatty degenerations may be caused by local disturbances in nutrition, if not too sudden. This is seen in cases of congestion, thrombosis, embolism, atheroma, in tumors, and in tuberculous and syphilitic deposits. The fatty changes of senility are probably of like origin. In the involution of tissues, as in the thymus, corpus luteum, uterus, etc., fatty degenerations are common. Trophic disturbances produce the degeneration, as is seen in the voluntary muscles. In many pathological processes, as in caseation, liquefaction necrosis, and the resolution of pneumonia, this metamorphosis plays an important rôle. In rare instances, as mentioned, fatty infiltration may pass into fatty degeneration.

Pathological Anatomy.—Organs the subject of marked fatty degeneration are often somewhat increased in size; to this, however, there are many exceptions: a notable one is acute yellow atrophy of the liver. The consistency is usually lessened, though associated fibrosis may render the affected part abnormally dense. The specific gravity of the



Fig. 13.—Fatty degeneration of the epithelium of the renal tubules; stained with osmic acid (Simmonds).

tissue is notably reduced. In the nervous system and in caseation and allied conditions liquefaction may occur. The color in typical instances is a pale yellow; the existence and degree of congestion, pigmentation, jaundice, or other associated conditions will obviously alter the color. The areas of degeneration may be uniform or isolated. In the heart and liver particularly streaks or irregular areas may produce a mottled appearance. On section, free fat may drip from the knife and cut surface; in other cases no fat-droplets can be seen macroscopically. In rare instances fat-crystals may be visible to the naked eye.

Microscopical Appearances.—*The parenchyma cells are first and most extensively affected, though the connective tissue may become involved. The cells are usually somewhat enlarged. The natural granules of the protoplasm disappear, and in their stead are fine dark granules, which usually stain black with osmic acid (Figs. 13, 14), and which are dissolved by alcohol, ether, etc., but not by acetic acid. A peculiar reaction of the granules is their staining with fuchsin (fuchsinophile granules). Usually the granules are very fine and only slightly refractile; they may, however, be large, and considerable droplets may appear or the entire cell become one large fat-drop, as in fatty infiltration.*



Fig. 14.—Fatty degeneration of the heart muscle.

The nuclei in many cases of moderate degree show no changes; later in the process, however, the chromatin becomes diffused and refuses to stain and the nucleus may entirely disappear. When the fat is dissolved out of the cell a vacuolated protoplasm may be observed. In early stages the protoplasm has been asserted to be unaltered when thus examined. The cell membrane sooner or later breaks down, and the fatty contents and detritus fill the space. Cholesterin, lecithin, and fatty crystalline formations are often seen.

Seats.—Fatty degeneration occurs in nearly all tissues. The epithelial structures, especially the liver and kidneys, the heart muscle, and the central nervous organs are the tissues most frequently affected. As before stated, interstitial as well as parenchymatous tissues may be involved. The cellular constituents of exudates and transudates are also liable to the change, and the liquid may thus present the appearance of an emulsion.

Pathological Physiology.—Recent investigations tend to destroy the old theory that fatty degeneration results from a transformation of the protoplasm of cells into fat. Investigations have shown that the cells of many of the tissues and organs, notably glands, contain fat, and that this is undoubtedly derived from the blood, also that the fat in true fatty infiltration has the same origin. In so-called fatty degeneration the protoplasm is diseased and in advanced stages completely destroyed. This would seem to sustain the old view of direct transformation of protoplasm into fat; but the most accurate chemical investigations do not confirm the possibility of such a transformation. Further, when animals were poisoned with phosphorus and a fat foreign to the animal was administered the fatty organs contained the foreign fat. These considerations have led to a quite general belief that fatty degeneration results from an infiltration of fat derived from the blood and remotely from the fat deposits of the body or from food. The significant difference between fatty infiltration and fatty degeneration is that the former is a deposition of fat in otherwise normal cells as a result of excessive supply of fat, or possibly a lowered metabolic activity which normally disposes of fat, while the latter represents a deposit of fat in a diseased cell, the disease inviting the deposition or greatly reducing the capacity of the cell to dispose of fat even in normal quantities. For these reasons the terms "fatty infiltration" and "degenerative fatty infiltration" have been suggested for the respective conditions. It seems certain that to some extent at least the granular and molecular fat contained in cells the seat of "fatty degeneration" represents normal fat of the cells which had previously been in some form of combination and invisible, but as a result the degeneration became free and visible. This view has been expressed by a number of pathologists and has some experimental support.

In some experiments in which starving frogs were poisoned with phosphorus the direct conversion of protoplasm into fat seemed to have been demonstrated, but even in these experiments the glycogen of the liver may have been the source of the fat produced, and, besides, ob-

jection has been raised against the chemical methods relied on in these experiments.

It would seem probable that both factors may be active in some cases, but Wells maintains that in kidneys and muscles the metamorphosis of intracellular fat is more important than absorption. In either case it is to be assumed that the enzymic power of the cells has been damaged.¹

Fatty degeneration tends to cause secondary changes in the protoplasm of the affected cell, or the degeneration which in the first instance underlies the condition tends to increase until the cell is practically destroyed. Cellular function is, therefore, eventually impaired or perverted, but experiments have shown that considerable fatty degeneration of the heart muscle may exist without impairment of the heart's power (Romberg, Krehl). The same may be true of other organs. Mild grades, with preservation of the nuclei of the cells, admit of recovery; severe grades go on to total necrobiosis.

Lipoid metamorphoses are found either as infiltrates or degenerations in cancer necroses, atheromatous blood-vessels, and syphilitic lesions. They were formerly considered fatty, but it is now strongly suspected that they have to do with protein destruction. The lipoids are commonly found as cholesterol esters and appear as doubly refractile or cuboidal crystals under the polarizer.

THE ALBUMINOID DEGENERATIONS

The hyaline, mucoid, and colloid degenerations represent protein metamorphoses which are closely related. In typical instances they can be quite clearly differentiated from each other, and for the sake of clearness and convenience they will be separately described. It must be understood, however, that the products are closely related substances whose chemical characteristics and relations are not clear, and which cannot in many cases be distinguished.

HYALINE DEGENERATION

Definition.—This term probably comprises a group of retrogressive processes characterized by the appearance of a clear, firm, homogeneous protein substance of obscure nature. It is probable that various processes, defined as hyaline, may have entirely different characters.

¹ A. E. Taylor while engaged in systematic analyses of the liver and kidneys in fatty degeneration noticed that these degenerated organs retained less of their fat on etheral extraction than do normal organs. He, therefore, carried out experiments on frogs by producing a fatty degeneration with phosphorus and extracting the fat, which was then compared with that from normal frogs. As a result of his experiments he offers the hypothesis that the combined fat is a metabolic constituent of the protoplasm of the cell. During the course of the disease causing the fatty degeneration this combination is broken after the manner of the action of ferments, and the previously combined fat is set free, when it appears as fatty granules in the protoplasm. Following this comes fat transportation and infiltration of the affected cells. The reason for such infiltration is, however, not understood.

Certain cases are allied to amyloid, mucoid and colloid metamorphoses, and some to coagulation necrosis. The hyaline change of epithelium of older authors is now, by general consent, classed as a mucoid transformation.

Etiology.—Hyaline degeneration occurs under the following pathological circumstances: in the muscles during infections and septic processes and following traumatism; in intoxications, as by lead; in interstitial hemorrhages and hematoma; in struma; in cicatrices; in the blood-vessels in old age, arteriosclerosis, or aneurysm; in all forms of *arteritis*, especially in *vessels of the nervous system*; in the endocardium and cardiac valves in all diseases affecting them; in the *granulomata*; in neoplasms, especially *cylindromata* and *keloids*; in the lungs in pneumonia; in the

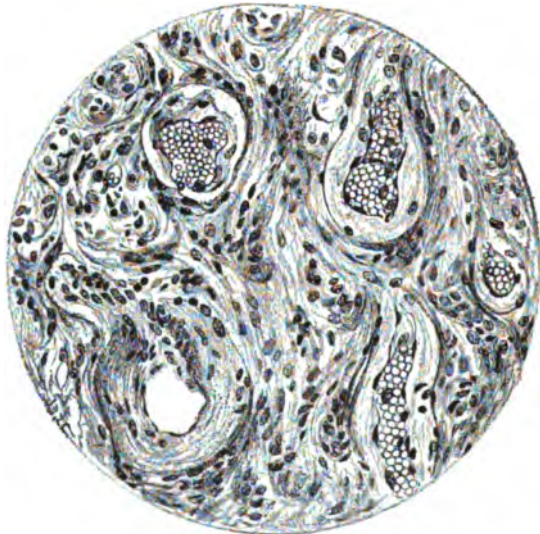


Fig. 15.—Cylindroma, showing a number of blood-vessels whose walls have become converted into hyaline material.

kidneys in nephritis; and in all conditions of coagulation necrosis and fibrinous exudation, for in these processes hyaline degeneration seems to be a factor. Very probably the process is not the same in all of these cases, but the similarity of appearance, staining reaction, and general pathological behavior prevents a definite differentiation.

Pathological Anatomy.—Hyaline change is not usually massive enough to be macroscopically appreciable. When so, the organ or tissue is enlarged, dense, and presents a pale, homogeneous, opaque appearance. Upon the mucous and serous membranes small collections may be readily seen, and may present either a pseudomembranous appearance or may occur as opaque plates upon or beneath the surface. Microscopically, there are three chief sites: (a) In the blood-vessels, where the degeneration may appear in the endothelium, beneath it, between the

coats and fibers of the vessel, or surrounding the vessel. The wall is thickened, the lumen is narrowed or obliterated; the endothelium may be loosened or in a state of proliferation. Perivascular hyaline change is well seen in certain tumors—*cylindromata* (Fig. 15). (b) In the interstitial tissues, as between the muscle-fibers, the hepatic cells, the renal tubules, in the reticulum of lymph-glands, in the retina, and in neoplasms and cicatrices. It may be uniform in distribution, but is more often irregularly clumped or may be in concentric whorls. In tuberculous foci the reticular fibrillæ become swollen and gelatinous in appearance. They may swell to such a degree that the whole focus has a uniformly waxy appearance, the cells enclosed in the meshes meantime undergoing complete necrosis. In sclerosis, as in the liver, the newly formed connective tissue may assume a hyaline character, the fibers being so closely packed together and transformed that the mass has a homogeneous appearance. (c) Within the cells. This condition is probably limited to mesodermic cells. It may be seen in muscle and giant cells, and in endothelium, leukocytes, or wandering cells to a less degree. Whether the epithelial cells take part in this transformation in the coagulation necrosis of mucous membranes and in the production of casts in nephritis has not been decided. It has not been possible, in the intercellular or interstitial varieties, to decide whether the substance was formed there or deposited there; in the vascular form, and especially in coagulation necrosis and fibrinous exudations, it is probable that it is formed *in loco*.

"Hyaline thrombi" cannot be distinguished in their appearance from hyaline masses elsewhere. Whether or not they are examples of true hyaline material is uncertain.

Russell's Fuchsin Bodies.—These are round bodies, of variable size, situated within or between the cells of epithelial tumors or many normal tissues. They resemble hyaline material in appearance and staining reactions, especially in their affinity toward acid fuchsin.

Unstained, hyaline substance has a glistening, waxy appearance; it is less translucent than amyloid. Typically it evinces an affinity for the acid anilin stains. Stained with van Gieson's mixture of picric acid and acid fuchsin, the hyaline substance takes on a brilliant red color. It may or may not take the fibrin stains; it often takes basic stains in a modified manner. In truth, the reactions of hyaline material are very uncertain and shifting: in many instances it can scarcely be distinguished from amyloid, and the change is then called hyalo-amyloid; in other instances the product closely resembles mucin and the colloid substance. The cells of affected parts often show fatty degeneration or other alterations.

Seats.—The locations most often affected are the muscles, especially the *recti abdominalis* in typhoid or other fevers, the mucous membranes, the liver, kidneys; ovaries (corpora lutea in particular) and adrenal bodies, the cardiovascular system, the nervous system, the serous membranes, and the retina and choroid coats of the eye. The other locations are suggested in the discussion of the etiology.

Pathological Physiology.—Von Recklinghausen believed it to be a coagulation of normal protein upon the death of the cells; this explanation is, however, insufficient. It appears more likely either that it consists of protein modified *in loco* by disturbed action of cells, or that it is a deposition by cellular carriers of insoluble material formed elsewhere. The exact nature of the transformation is entirely obscure; it cannot be held analogous to the coagulation of proteins by heat; nor to the precipitation by metals or salts, since in these events the proteins are not usually rendered permanently insoluble in water and are in other ways clearly different. Hyaline material can undoubtedly be reconverted, absorbed, and removed. Its presence rarely compromises the parenchymatous structures to an extreme degree.

MUCOID DEGENERATION

Definition.—Theoretically, this is the conversion of cellular protoplasm into mucin. Mucin is a glycoprotein which contains no phosphorus, and which by virtue of its carbohydrate moiety reduces cupric sulphate in alkaline solution. Chondroitin sulphuric acid has been found in some mucins, showing the relationship of this albuminoid degeneration to amyloid infiltration. It is quite insoluble in water, but has itself a marked capacity for taking up water. It is very soluble in alkaline solutions, but is precipitated by saturations with most neutral salts. It is precipitated by acetic acid from solutions poor in salts; also by heat, alcohol, and many of the metals. It does not dialyze. The secretions from different classes of epithelium differ notably among themselves, and the pathological mucins differ still more.

Etiology.—Mucoid transformation should be distinguished from hypersecretion of mucin. Hypersecretion is a common result of inflammation or irritation of all sorts; it is seen in the pulmonary, gastrointestinal, and urinary mucous membranes, in the glands of Cowper, the gall-bladder, the salivary glands, in the antrum of Highmore, in the lacrimal glands, and in the testicles. The product of the epithelium of the urinary tract and gall-bladder, usually called mucin, is more often nucleo-albumin. Mucoid degeneration, in the strict sense, occurs most frequently in mesoblastic tissues, the abnormal substance lying between the cells. It is in some way connected with inflammatory processes, as, apart from its occurrence in tumors, it is found only in tissues the seat of inflammation. Any of the connective tissues of the body may be affected. Widespread myxomatous degeneration of the subcutaneous tissues may be seen in myxedema. In some cases of myxedema, scleroderma, and the other pachydermic affections mucin has been extracted from the skin; other attempts in similar cases have failed. Neoplasms comprise the third group of conditions presenting mucoid phenomena. The transformation occurs in sarcomata, carcinomata, fibromata, lipomata, chondromata, and especially in the myxomata, in which mucin is the essential element, while in the other growths it is an accidental and occasional transformation. In the epithelial tumors the epithelial cells themselves may be affected.

Pathological Anatomy.—The gross appearances may consist in nothing but the appearance of the mucin. Upon catarrhal mucous membranes is a coat of thick, tenacious mucus, with or without congestion or other changes. In localities where the mucin becomes pent up it swells markedly, dilates the containing spaces, flattens the epithelium (which may then atrophy), and later becomes converted into a simple albuminous fluid. Such a process is seen in the antrum of Highmore, in Cowper's glands, in the salivary glands, in the gall-bladder, in the vermiform appendix, etc.; in these cases the appearances are those of a cyst. In mucoid degenerations in the connective tissues the appearances are often not characteristic of mucin; the tissues are soft and elastic and tear easily. In tumors, cysts are usually formed along with diffuse mucoid infiltration. In cystic ovarian neoplasms the production is often massive, and the substance is often peculiar in refusing precipitation by acetic acid, and has, therefore, been termed "pseudo-mucin." In myxomata the substance is usually much more dense.

Microscopical Appearances.—In catarrhal mucous membranes the goblet-cells are seen in excessive quantity. Only in extreme instances is the process accompanied by the death of the cell. The cells are much swollen, and the distal end is especially bulged out with its drop of mucin. There is usually a sub-mucous inflammatory reaction, and pus-cells containing mucoid material may be seen. In the connective tissues it is seen that the mucin lies between the cells and that the ground substance has disappeared—*i. e.*, been converted into mucus (Fig. 16). The cells very rarely present mucous change, but are often degenerated in other ways. In tumors the change may occur in and between the cells and in the form of cysts, whose walls may or may not present a cellular lining. The blood-vessels are rarely affected. In all situations mast-cells may be seen, often abundantly.

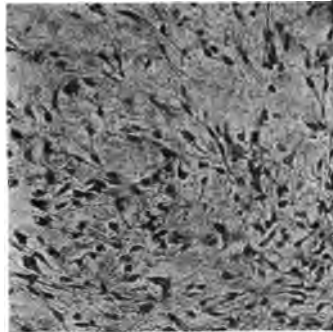


Fig. 16.—Myxomatous degeneration of a sarcoma, showing stellate cells separated by mucoid intercellular material (Karg and Schmorl).

Mucin is best fixed with corrosive sublimate. As a rule, it elects basic stains. It stains only moderately with hematoxylin, but very well with methylene-blue and, indeed, with most of the basic anilin stains. Thionin and toluidin-blue are the best stains, giving it a purple-red color. These staining reactions are not entirely distinctive, and it is often impossible to differentiate mucoid from colloid material, and even from hyaline and amyloid material.

Seats.—Of normal epithelial tissues, the mucosa of the respiratory and gastro-intestinal tracts, the salivary glands, and the uterus are most often affected; any epithelium may, however, be involved. The connective tissues have been sufficiently considered. Of neoplasms, ovarian

cysts, abdominal carcinomata, and mesoblastic tumors anywhere are most liable.

Pathological Physiology.—Since the deposition of mucin seems to be excluded, the only explanation is to assume the conversion of other proteins into mucin. The causes and *modus operandi* are not clear; the fact, however, that in the cysts the mucin may be reduced to simple albumin shows the possibility of such transformations.

Unless the disease is very prolonged, affected mucous membranes may recover. The connective-tissue forms do not of themselves threaten the life of the tissue; and the deposit is often removed by reabsorption. In neoplasms the degeneration seems an evidence of cell death.

COLLOID DEGENERATION

Definition.—This consists in the abnormal appearance of a substance whose physical prototype is the colloid material of the thyroid gland. It is not precipitated by acetic acid or alcohol, does not take up water avidly, and is, therefore, much like the pseudomucin already noted.

Etiology.—It occurs in goiters and in thyroid neoplasms, in the hypophysis cerebri, in the kidneys (some cases of congenital cysts) and the adrenal bodies, in the prostate and seminal vesicles, in the atrophic gastric mucosa, in cysts of the lips and larynx, and in the cervix uteri. Colloid transformation in neoplasms apart from those of the thyroid body is very rare. The natural and increased colloid of the thyroid gland, and sometimes that found in the hypophysis, contains iodine, associated with a globulin and a nucleoprotein. Because of the absence of iodine in other so-called colloid conditions, cancers and cysts, many authorities restrict the word "colloid" to the iodine-containing kind of the thyroid, and call the homogeneous metamorphosis in cancers mucoid. Colloid is believed to be a direct product of altered cell metabolism, and, aside from the thyroid, is usually mucin, pseudomucin, or some other protein which has assumed a jelly-like form in a tightly closed space. There is no uniform organic chemical substance that may be identified as colloid.

Pathological Anatomy.—Affected organs may be enlarged and may be hard or quite soft. On section, the colloid areas appear as yellowish-brown, translucent bodies; rarely they are arranged in large clumps. They may be macroscopically invisible or, on the contrary, may form large cystic collections with thin, flattened walls. Colloid degeneration may be accompanied by serous transudation, due probably to vascular disturbances. The serous transudation seems to dissolve the colloid material, so that finally the cysts form compartments filled with a chocolate-colored fluid containing pus, blood, and crystals of cholesterol, sodium chlorid, and calcium oxalate (Fig. 17).

Microscopically, the material is found in the glandular acini, in the cells, and in the connective tissues. There are often signs of pressure, and, probably from the same cause, the areas are anemic and have

a poor vascular supply. The arrangement is usually in balls or whorls, homogeneous as a rule, but often with concentric or radiating lines. The areas often intercommunicate, and extensions may be traced into the adjacent tissues. The cells usually show degenerative changes, and inflammatory reactions are often present. Crystals of calcium oxalate are common. Acid stains are usually elected, as in hyaline degeneration. The indefiniteness of the reactions may make it impossible to exclude hyaline and mucoid changes.

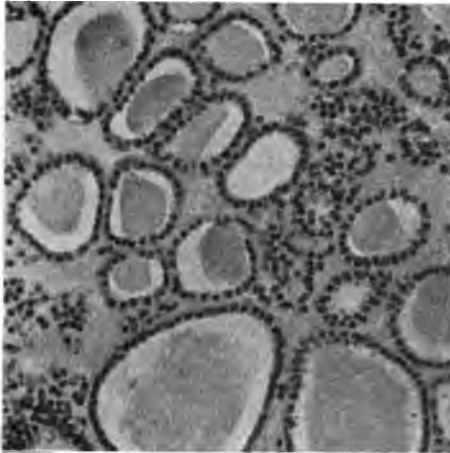


Fig. 17.—Colloid degeneration of the thyroid gland, showing masses of colloid matter in the gland acini (Karl and Schmorl).

Pathological Physiology.—This is obscure, but seems to be analogous to that of mucoid change. The substance is undoubtedly produced *in loco*.

Colloid is a grave degeneration, usually connected with marked cellular disturbances.

AMYLOID INFILTRATION

Definition.—Amyloid deposits are nowadays thought infiltrative, although formerly regarded as degenerative. Amyloid, a name given by Virchow because of certain reactions suggesting starch, is not a starch, but a glycoprotein, an abnormal combination of chondroitin sulphuric acid, such as is normal in tendon, with a protein. The exact chemistry is not known and the combination is believed to be due to faulty metabolism *in loco*. It differs from most retrogressive changes in that it affects the interstitial tissues, and not the cellular contents. The presence of balls of amyloid within cells has been maintained by some authors. The names “lardaceous disease” and “lardacein” are used by some writers, denominations warranted by the gross appearance at least. Amyloid disease may be local or general, the latter being called “amyloidosis.”

Etiology.—The common conditions under which amyloid infiltration arises are prolonged suppuration and ulceration. In tuberculosis, especially of the lungs and skeleton, particularly in cases of mixed infection and in syphilitic ulceration, are found the conditions most favorable to its production. It occurs, however, in connection with ulcerations of various sorts, gastro-enteritis, and actinomycosis. Rarely it occurs under conditions of cachexia without suppuration, as in cancer, malaria, leukemia. Sometimes it is found without any apparent cause.

Certain local "amyloid" formations (*corpora amylacea*) are probably in nowise connected with the general condition and, undoubtedly, are often entirely physiological. Their relation to amyloid disease is doubted by many, but they do give modified iodine and gentian-violet tests. It is said that they grow by deposit of crystals containing some protein.

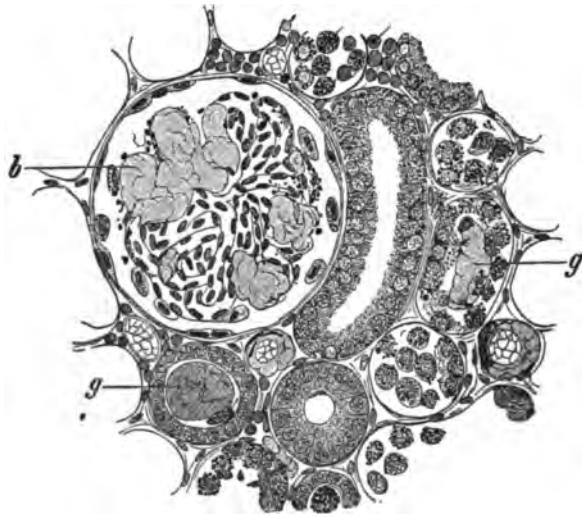


Fig. 18.—Amyloid degeneration of the kidney, showing amyloid substance in the walls of the blood-vessels of the glomerulus at *b*, and hyaline tube-casts in the renal tubules at *g, g* (Ziegler).

Pathological Anatomy.—In marked instances the organs are enlarged and their specific gravity increased. On section, the tissue is firm; the cut surface is smooth and neither contracts nor extrudes. The consistency varies with the coexistence and degree of fibrosis, fatty degeneration, etc. Amyloid substance is more inelastic than any other infiltrative material. The color of the organ is usually pale, but may obviously be altered by congestion, pigmentation, or fatty degeneration. The amyloid substance itself has a glistening, waxy, translucent appearance which is almost pathognomonic. This waxy appearance is not always uniform. Slight or even moderate degeneration may not occasion macroscopical appearances; in fact, apparently quite normal tissues may

be highly amyloid microscopically. The special appearances in various organs will be described in the appropriate chapters.

Lipoid or actual fatty deposits are found associated with amyloid infiltration, especially in syphilitic conditions. They are either deposits from body fluids or arise from tissue degenerations in the vicinity.

Microscopical Appearances.—The favorite seats are the outer surface of capillary blood-vessels and the intima and media of larger blood-vessels, the adventitia being rarely affected, the endothelium apparently never. The fixed connective tissues of the organs, elastic tissues, and basal membranes of glandular acini, or between them and the gland cells, are the parts affected, the wandering cells and leukocytes being rarely involved. Muscle cells are undoubtedly susceptible; but recent studies seem to show that glandular and lining epithelium is never involved. Such cells may, and often do, show fatty or other degenerations or necrosis, but the presence of amyloid substance within their protoplasm has not been shown. The substance appears as irregular clumps or streaks in the interstitial tissues, often compressing the cells and blood-vessels. It presents a glistening, homogeneous appearance. The cells usually present evidences of atrophy and other degenerations. In the renal glomeruli and in the Malpighian corpuscles of the spleen the appearances are perhaps most distinctive. Without staining, amyloid degeneration cannot always be distinguished from other degenerations; indeed, not always with staining reactions. The substance is highly resistant to bacterial decomposition and to digestion.

Reactions.—(See also below.) The gentian-violet reaction seems to be the most invariable. In sections of tissue fixed (preferably in alcohol) for microscopical study gentian-violet colors the normal tissues blue; the amyloid substance is a light pink or red. Iodin-green gives a similar red reaction. A mahogany-red reaction with Lugol's solution of iodine is quite constant, but fails in the isolated amyloid bodies. It is easily obtained in fresh specimens freed of blood. The red color is changed to a blue by treating with sulphuric acid or chlorid of zinc.

Seats.—In the order of frequency amyloid degeneration affects the kidney, liver, and spleen, then the larger blood-vessels, the intestinal mucosa, the lymph-glands, the skeleton, the adrenal bodies, and the heart. It rarely affects the pulmonary mucosa, the bladder and genitalia, the thyroid body, the voluntary muscles, and, apart from the local amyloid bodies, the nervous system or the integument.

Local Amyloid Formations.—These occur in the nervous system, especially in advanced years and in scleroses, grouped about the blood-vessels, and most marked in the posterior cord and in the brain; in the prostate gland; about inflammatory areas; in infarcts; in granulomata, especially syphilis; as tumor-like swellings in the upper air-passages, and in neoplasms. They present themselves as small round bodies which usually have a concentric arrangement resembling starch granules. They do not usually present the typical amyloid reactions; often they react more like hyaline substance, and, indeed, the blood-

vessels of the affected part seem especially affected with hyaline change. Ribbert says the small vessels are curiously free from change. The neighboring lymph-vessels and glands are usually attacked. The special appearances and reactions of the amyloid bodies of the nervous system will be described in connection with Neuropathology.

Pathological Physiology.—As stated, amyloid substance seems to be a combination of chondroitin sulphuric acid with a protein. It is composed of hydrogen, nitrogen, carbon and sulphur, and is insoluble in weak alkalies. Chondroitin acid is normally present in bones, cartilages, and elastic tissue. It seems to have been shown that an amyloid-like substance exists in the elastic coat of the blood-vessels—perhaps a different combination of chondroitin acid. Our present knowledge suggests that amyloid substance is not entirely abnormal, but rather an abnormal combination of normal substances. It seems to result from protein alterations in connection with the pathological processes already detailed, having as a result the liberation of large amounts of chondroitin sulphuric acid. That bacterial influences are not necessary is suggested, though not proved, by the fact that amyloid change has been produced by long-continued aseptic suppuration induced by turpentine injection. Amyloid change is an infiltration, the constituents being deposited from the blood and assuming their peculiar characters locally, for amyloid is not found preformed in the blood itself. Possibly local cellular conditions favor the deposition by reason of a loss of power to dispose of the constituent substances brought by the blood. Hyaline degeneration seems at times a preliminary stage in the process.

Amyloid degeneration interferes with functional activity by pressure upon the parenchyma and by vascular disturbances. By its situation in and around the blood-vessels it may occasion thrombosis. Reabsorption of amyloid substance is possible, as it has been known to occur when part of the diseased area has been extirpated. Such reabsorption does not, however, occur when extensive amyloid change exists.

GLYCOGENIC INFILTRATION

Definition.—This condition consists in the presence of glycogen in cells which normally contain none, or the presence of an excess in cells which normally contain it, as in the liver, cartilages, muscles, leukocytes, in the embryo in all tissues, and in the uterus. The attempt has been made to separate glycogenic infiltration from a glycogenic degeneration, but the conversion of protoplasmic protein into glycogen has never been demonstrated.

Etiology.—The condition is not infrequent. It is seen in the tissues in diabetes, especially in the kidneys (Henle's loop in particular), muscles, liver, and circulating leukocytes. It occurs in neoplasms, especially in malignant growths of mesoblastic origin, being rare in most carcinomata. It may be said that the more cellular the tumor, the more the glycogen, except in carcinomata, where the amount is small and variable. In leukocytosis of different varieties the cells may con-

tain granules of glycogen or a substance resembling glycogen, and similar granules may float free in the plasma (see Iodophilia). In purulent collections and in inflammatory areas the cells may be markedly infiltrated. The infectious granulomata, however, seem exempt. The amylaceous bodies of the prostate are closely allied to glycogen.

Pathological Anatomy.—Tissues rich in glycogen may present a hyaline appearance; usually there are no macroscopical alterations. Microscopically, the material is generally found within the cells; it may, however, be in the intercellular substance, and may be free in the plasma of blood or the fluid of exudates. It is commonly deposited as round balls, which may be concentrically striated. In fresh tissues it is soluble in water, but loses its solubility after fixation by alcohol, etc. Tissues to be studied for glycogen must be fixed in absolute alcohol, since watery solutions add a molecule of water to the glycogen and change it to sugar,



Glycogen is stained brown by iodine, but the brown is not turned blue on the application of sulphuric acid. Ptyalin or amylopsin converts glycogen into sugar, with the loss of the color-reaction.

The **pathological physiology** is obscure. In diabetes it is simply an expression of the general hyperglycemia. At the end of long exhausting diseases glycogen may not be found in the cells. The cells are left swollen. In neoplasms and suppurations the collections are probably depositions.

DROPSICAL INFILTRATION

By dropsical infiltration is meant *edema of the cells*, the presence in cells of an excess of plasma. It may be considered as of two kinds:

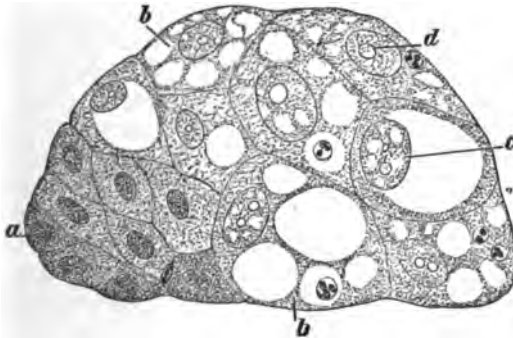


Fig. 19.—Dropsical infiltration of the epithelial cells of a carcinoma of the breast: *a*, Ordinary epithelial cells; *b*, *b*, dropsical cells; *c*, dropsical nuclei; *d*, enlarged nucleoli (Ziegler).

(*a*) Dropsical degeneration, a fine granular disintegration of the cytoplasm preceding or associated with cloudy swelling. (*b*) Dropsical infiltration, grosser collections of vacuoles or droplets of fluid disturbing the general architecture. This does not always occur in general dropsy,

the fluid being between the cells and often compressing them to a marked degree. In other instances the cells take up the fluid. In burns and pemphigus and in other skin lesions presenting vesiculation, and in various inflammations of organs, edema of the cells occurs. It is also a part of the degeneration termed "cloudy swelling."

The cells are enlarged, often to an extreme degree, and they may even burst. The protoplasm sooner or later becomes cloudy and often presents degenerative changes—fatty metamorphosis in particular. Vacuolation is frequently observed (Fig. 19).

The condition is probably a purely physical phenomenon in the dropsies. In the cutaneous lesions other factors are operative. The diffusion of water into the cell may be explained by a toxic disturbance of the internal chemistry with an increase of crystalloids which attract water.

CALCIFICATION

Definition.—Calcification consists in the abnormal deposition in tissues of earthy salts, without organization and the anatomy of bone. It may be considered as evidence of local or general senescence, but is never a primary process. The phosphates and carbonates of calcium are the chief salts concerned; oxalates, however, are often present; and the corresponding magnesium salts may be mixed with them. The best physiological examples are the senile change in the vascular apparatus and the formation of the brain-sand (*acervulus cerebri*). Calcification of the skeletal tissues is usually accomplished as a physiological process through the activities of special cells; this is an essential element in ossification.

Etiology.—The deposition generally occurs in diseased tissues, especially in those the seat of vascular disorders. Local necrosis or fibrosis antedates intercellular calcification, and the process may be accompanied by atrophy and absorption of certain cellular elements. In neoplasms, abnormal cellular conditions certainly predispose; but here, too, the vascular relations are of notable importance. Hyaline and fatty degenerations often precede or accompany calcification.

In rare instances no local predispositions can be determined. Cases of this kind occur in old age, and in these cases it is inferred that, owing to increased lime-resorption from the skeleton, the system is saturated to the point of precipitation (metastatic calcification). Similar supersaturation of the blood with calcareous matter may occur in cases of extensive disease of bones, and may lead to widespread deposition. It is noteworthy that the precipitation of the bone salts circulating in excess occurs most frequently where acid is excreted—lung, stomach, and kidney. Local anemia favors calcification.

v. Kossa found that corrosive sublimate, acetate of lead, copper salts, iodine, and iodoform all are capable of producing calcification experimentally.

Pathological Anatomy.—Early in the process no macroscopical signs are apparent. On microscopical examination the salts are seen as fine gran-

ules scattered through the *intercellular* substance. Cellular infiltration, however, is not uncommon, and in such instances the cells show more or less extensive nuclear and protoplasmic degenerations. By the coalescence of the granules larger, irregularly spherical bodies may be formed. These usually have a concentric arrangement (psammoma bodies). Definite crystals are rare, but may be seen. The next adjacent tissue may present an opaque appearance. In certain localities, especially the blood-vessels and serous membranes, calcareous plates are formed. The depositions may attain a surprising size, especially in the vessels and in neoplasms. The color of the deposits is usually white, grayish, or yellow; accidental pigments may, however, produce discolorations. On staining, the deposition takes up both carmine and hematoxylin, but exhibits no elective attraction for the anilin dyes. The salts are dissolved by acids, best by hydrochloric acid; in the case of carbonates, with evolution of carbonic acid gas. Fibrosis, cellular necroses, and degenerations can be demonstrated in the tissues by suitable methods.

Seats.—It is in the cardiovascular system that the condition is of the most importance. It often occurs as a simple senile change, usually connected with an atrophy of the elastic tissues of the vessel walls, hyaline degeneration of the connective tissue, and general fibrosis. It is almost invariably an accompaniment of sclerotic endocarditis and arteriosclerosis. In the endocardium the valves are most frequently affected; of the vessels, the aorta, the coronary arteries, and the cerebral vessels. The process is, however, often universal, and the splanchnic vessels and radial arteries seem very susceptible. It affects chiefly the intima and media. In the pericardium the deposition is uncommon without the previous occurrence of pericarditis; in adherent pericardium the heart may be literally enclosed in a calcified sac. In the myocardium calcification is usually interfibrillar, but may involve the fibers. Large collections may occur in the pituitary body, the meninges, and in the ventricular plexuses. It is common in the joints, uncommon in the pleura, rare in the peritoneum. In the muscles local formations are not rare, and usually occur at the seat of previous injury or irritation. In the lungs and liver it is not unusual in and around foci of necrosis due to various causes (tuberculosis, parasites, etc.). Cicatricial tissue often becomes calcified. In the walls of cysts, in the biliary and urinary bladders, in the limiting wall of old abscesses and hematmata, in thromboses, and even in cutaneous scars calcification, as a crust or infiltration, is a common incident. In the kidneys infarcts of these salts may be formed. The neoplasms most subject are the avascular tumors: uterine fibromata, fibromata in general, dermoid cysts, goiters, scirrhus carcinomata, tumors of the pituitary bodies, and especially neoplasms involving bones or cartilages. It may, however, occur in the most vascular sarcomata. The special term "psammoma" (*q. v.*) is applied to certain calcified neoplasms. *Lithopedia* are the calcified fetuses of extra-uterine pregnancy. Apart from neoplasms, the most striking intracellular depositions are seen in the ganglion-cells in areas of softening and in the renal cells

following certain metallic poisonings (mercury). It is interesting to note that the intestinal epithelium, which normally secretes the larger part of the lime-salts discharged from the body, is rarely infiltrated by them.

Pathological Physiology.—It seems probable that calcium is carried in the blood, in the form of tribasic calcium carbon phosphate, by the agency of the proteins with an appropriate amount of carbon dioxid. In both normal and pathological bone salt deposit there seem to be two forces at work, a local chemical condition favoring the precipitation of the least soluble crystalloids from the blood and the existence of some tissue element having an affinity for calcium. The latter factor has been said to be phosphoric acid by some writers and ascribed to physical factors, such as the concentrated colloid of cartilage, by others. The local chemical changes favoring calcium deposit are said to be a decrease in protein concentration when the tissue pabulum is thoroughly used up *in loco*, and increased alkalinity with decreased carbon dioxid. There is, however, some experimental evidence to show that the fatty acids formed in necrobiotic tissue combine with calcium to form soap, the combined acid later giving way to acid radicals of stronger affinity for the base, carbonic and phosphoric. It must not be forgotten that we are dealing with a secondary process in a tissue whose metabolism is not and has not for some time been normal.

Calcareous deposits are probably never removed, but once formed, remain permanently. There is no doubt that they influence the adjacent tissues, causing degenerations.

OSSIFICATION

This term implies the deposition of lime-salts and other changes through the agency of osteoblastic cells. It occurs in cartilages and in tumors connected with the bones, cartilages, and periosteum. Ossification of the muscles may occur as a local process or as a widespread and progressive disease. (See Myositis Ossificans.) The salts are regularly deposited and are usually in masses between the cells. An accurate differentiation from calcification can in some instances be made only by the detection of osteoblasts after decalcification of the material. The essential difference lies in the fact that in ossification an attempt is made to reproduce the architecture of bone.

URATIC INFILTRATION

Deposits of urate of sodium in the cartilages and fibrous tissues of joints and in various other situations occur in the course of gout. (See Disturbances of Metabolism and Diseases of Joints.) It is not known whether this occurs in normal or necrotic tissue, but such a deposit is not normal to cells. The urates occur as slender needles. In the kidneys of babies shortly after birth there occur deposits of urates, chiefly of ammonium, to which the name "uratic infarct" was formerly given.

This gives a false impression, since it is merely a collection of urates of which the kidney cannot rapidly rid itself.

Cholesterin deposits are not really infiltrations, but result from cellular degeneration, or some as yet undetermined cause. They appear in cysts and tumors, as in the thyroid and in atheroma, as flat, rhombic plates with an angular defect in one corner. With sulphuric acid they give first a red then a violet color.

Concrements.—There may collect in bodily or organ spaces, within the organs or their tubular entrances and exits, masses of inorganic matter. These are called concrements. By this is not meant that masses of foreign matter are introduced solely from without, like hair balls, but those whose components are recruited from the body fluids. Concrements may be started by a nucleus of desquamated covering or a product of inflammation, or by concentration, inspissation, or precipitation of some otherwise normal secretion or excretion. The first is exemplified by the collection of mineral salts around a bit of vesical mucosa that has been separated from the bladder wall or around a mass of bacteria clumped in the gall-bladder by the bile, and floating in it. The second type is exemplified by collection of urates occurring as sand in the urine, with either clumping or growth by accretion. The so-called fecal stones arise by stagnation and inspissation of feces, with later accumulation of earthy salts. All stones probably have some organic matter in them either as a nucleus or caught in their growth. Small foreign bodies may penetrate viscera and cavities and form the nucleus of a stone. The chemistry of calculi varies with their origin. (See Urinary, Biliary, etc.) It has been suggested that the word "calculi" be restricted to bodies arising from precipitation of glandular secretion, and the word "concrements" to the deposits of calcareous matter locally in organ passages, leading to the formation of solid masses. This may be convenient, but is apt to lead away from the thought that a nucleus of some sort is necessary for concrements.

PIGMENTATION

According to the origin and variety of the pigments, pigmentations may be divided into four groups: 1, those in which the pigments are derived from external sources; 2, those derived from the hemoglobin; 3, those derived from the bile; 4, those derived from cellular activity within the organism.

Pigmentation from the Exterior

Of the first group, those caused by entrance of foreign bodies through the air-passages are the most important. The condition now generally termed **pneumonokoniosis** is commonly a disease of occupation. Coal, iron, and stone are the most frequent foreign substances inhaled. Vegetable particles, as grain-dust and textile fibers, and animal hairs and furs, are not uncommonly the cause of such pigmentations. Corre-

sponding to the agent, there are such terms as "anthracosis" (coal-dust pigmentation), "siderosis" (iron), "calcicosis" (stone), etc. (Fig. 20).

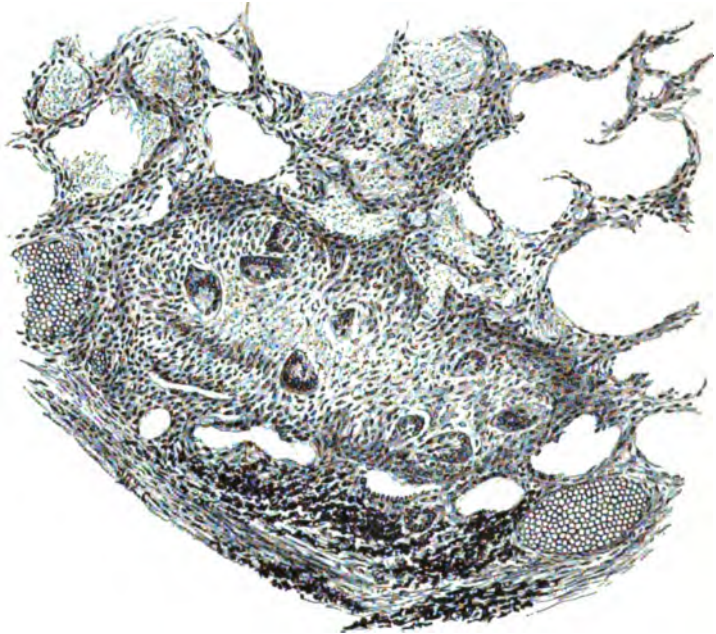


Fig. 20.—Tuberculosis of the lung, showing anthracotic pigmentations in the lower part.

Inhaled substances probably do not reach the alveoli, but are caught by the bronchial cellular cilia. In part they are coughed up or otherwise

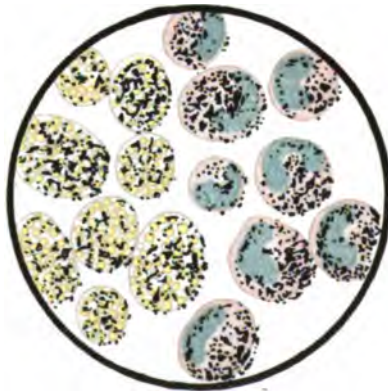


Fig. 21.—Phagocytic cells of the bronchial secretion (sputum) containing black particles of dust and carbon; the cells on the right are stained with methylene-blue (Jakob).

cast off with the bronchial secretions; in part they penetrate the bronchial walls or are carried by phagocytic cells into the submucosa (Fig. 21).

They may become deposited in the latter situation, or may be carried in the lymphatic circulation to the peribronchial and mediastinal glands, the fibrous tissue of the lung, or the subpleural tissues. In rare instances, supposedly by rupture or inflammation of a lymph-node, the pigment finally reaches the general circulation, following which it is deposited largely in the spleen, liver, intestinal mucosa, and kidneys. In such cases it shows a periarterial deposition in the secondary location.

Some investigators have attempted to explain anthracosis of the lungs by absorption of coal particles through the alimentary tract. They assert that the particles pass through the abdominal lymph-nodes, up the posterior chain into the mediastinum, and thence to the lung. They would use this reasoning also to explain the course of infection in pulmonary tuberculosis. The theory is not widely accepted.

Pigmentation through the alimentary tract is well illustrated by **argyria** following the excessive ingestion of soluble salts of silver. The depositions seem to consist of a reduced form of a silver albuminate. In the skin the pigment lies directly under the epithelial layer, between the cells, and in the intercellular tissue and lymph-spaces. The gastric and intestinal walls are deeply affected. The liver and kidneys are usually involved; in the former the deposition is periportal, in the latter the glomeruli and the corticomedullary boundary contain the pigment; in both the cells are free. Among the rarer sites are the choroid plexus, the various glands of the body, and the walls of the blood-vessels.

Pigmentation by cutaneous absorption apart from tattooing is problematic; it has been alleged to occur in workers in copper.

Hematogenous Pigmentation

This concerns the deposition of pigments derived from the hemoglobin, of which there are two groups, the siderous and the non-siderous. The chief siderous pigment is hemosiderin, which has, however, many modifications; the non-siderous pigments are derivatives of hematin—hematoidin, hemofuscin, melanin, etc. In the course of time the siderous pigments may lose their iron. Probably all formation and further elaboration of these pigments are the result of specific cellular activities. Two groups of hematogenous pigmentations may be distinguished: (1) those in which hemolytic agents act in the circulating blood or the associated organs, and (2) those in which the reductions occur locally.

(1) To the first group belong the general hemolyses. In pernicious anemia and leukemia, in malaria, in severe cachexias, in occasional infectious and septic processes, in poisonings (as by pyrogallie acid, chlorates, arseniuretted hydrogen, by some mollusks, by pyridin and toluylendiamin, etc.), the hemoglobin is set free in the circulation. It is promptly excreted by the kidneys, and to a limited extent by the intestines; much is converted into bile in the liver, some little passing into the bile unchanged. A certain amount is reduced by the tissues (apparently by the liver) to the two before-mentioned series of pigments, which are then carried in the lymphatic and vascular circulation,

and by means of cellular carriers are deposited in various places. As time passes, these pigments seem to become reduced, the iron being largely excreted by the intestine and the remainder by the kidneys as urobilin. In the liver the depositions are mainly in the periphery of the lobule; in the spleen, in the region of the follicles, and especially in the endothelium; in the kidney the most marked collections are in and about the glomeruli and the tubules. In all tissues the depositions are both intercellular and intracellular; the cells may either take up pigment or have it deposited in them.

Hemochromatosis.—Von Recklinghausen first described under this name a condition in which iron-containing pigment is deposited in the epithelia of the abdominal glands, especially the liver and pancreas, and iron-free pigment in the smooth muscle-fibers of the intestines, and the walls of blood-vessels and lymph-vessels, as well as in connective tissues. He found cirrhosis of the affected organs associated with the pigmentation. Later a form of widespread pigmentation of the same character and involving the structures named, as well as other organs, and notably the skin, and attended with glycosuria, was described by French writers under the name of *diabète bronzé*. In this condition there is pronounced cirrhosis of the liver and pancreas, and the diabetic association is attributed to the involvement of the latter organ. Cases without pancreatic cirrhosis of a certain grade or kind are unattended with diabetes.

Alcoholism, cachexia, and suppositious toxemias of other sorts have been regarded as of etiologic importance. The pigment is certainly of hematogenous origin, and is believed to be due to an altered metabolism in pigment-carrying proteins. The deposits in the cells cause degeneration and death of the latter and consequential cirrhosis.

The appearance of organs with marked hematogenous pigmentation varies with the variety and stage. A rusty-red color is the usual early appearance; later a brown, then a greenish, color may be produced, and finally a dark blackish brown. The association of jaundice, which is common, alters appearances very much.

(2) The two chief causes of *local pigmentation* are thrombosis and interstitial hemorrhage and coagulation. The pigmentations seen in the indurations resulting from prolonged venous stagnations and congestions are of analogous origin. Under these circumstances the hemoglobin is diffused from the blood-cells, and a portion passes directly into the plasmatic circulation and is carried away to be eliminated; soon, however, the area becomes walled off and the two sets of pigments are then formed within. The siderous pigments are most frequently seen in small lesions and at the periphery of large ecchymoses; the hematoidin series is most prevalent within the cystic contents. The pigments change in color (the color changes in a bruise are due to this), and finally become a brownish amorphous matter, which in turn disappears. Phagocytic cells take up all forms of the pigments (Fig. 22) and carry them to various parts of the body, especially to the liver, hematopoietic organs, intestines, and glands; the depositions in them are known as *pigment metastases*.

The distinctive reactions of the various pigments are not well known. Of hematin and hemin it is known that they are insoluble in water, alcohol, and ether; slightly soluble in weak acetic and mineral acids; easily soluble in chloroform and in weak alkalies, from which solution they are precipitated on the addition of lime- or baryta-water.

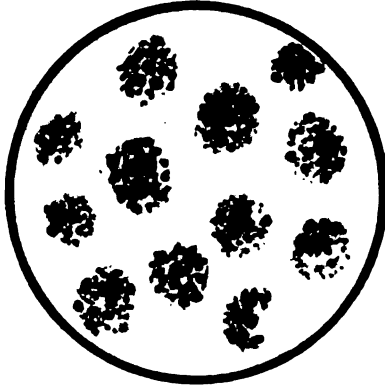


Fig. 22.—Phagocytic cells of the sputum containing blood-pigment, from a case of cardiac congestion of the lungs (Jakob).

Hematoidin differs from these in being somewhat soluble in ether, but insoluble in weak acetic acid, and gives with strong nitric acid the spectral play of colors. Apart from the iron reactions little is known of hemosiderin. The iron is best demonstrated by its conversion into the

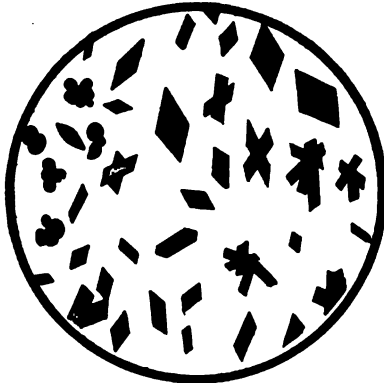


Fig. 23.—Hematoidin crystals from an old hemorrhagic focus (Jakob).

sulphid by means of ammonium sulphid, or by the Prussian-blue reaction with weak hydrochloric acid and potassium ferrocyanid (Perls' test).

Microscopically, hematogenous pigment presents three chief appearances: small needles, rhombic crystals, and amorphous masses or fine balls clumped together (Fig. 23). The first two forms are very

rarely seen within cells, the last form commonly. The colors vary from a pink-red to a deep rubin, from pale yellow-green to a deep brown or absolute black.

Hepatogenous Pigmentation

Pigmentations derived from the bile are due to bilirubin (isomeric with hematin) and its oxidation product, biliverdin. Jaundice ordinarily is of hepatic origin, but late observations would seem to indicate that bilirubin can be formed in the body without the action of the liver. The importance of this is not yet understood. Jaundice can also appear when a great hemolysis occurs, for if too much hemoglobin be thrown upon the liver, all the bilirubin cannot be discharged with the bile and is reabsorbed.

The presence of bile or its salts in the blood occurs as a result of external obstruction to the bile flow, or of internal mechanicochemical conditions favoring abnormal retention. The bile passes into the blood mostly by way of the lymph-channels, but may go into the vessels directly, as in cases of acute yellow atrophy. The bile-salts and pigments are both in the blood in icterus and are responsible for some toxic effects, such as degeneration of endothelium with hemorrhage and depression of the central nervous system.

The deposition of these pigments may be either in solution in the tissues, in granular precipitations, or in crystals (needles and rhombic plates). The cerebral substance alone seems never, except in the newborn, to be pigmented. The liver, skin, mucous membranes, the endarteria and other serous membranes, and the glandular and fatty tissues are especially susceptible. The color is first yellow and gradually deepens to a deep olive, the urine presenting similar transitions. The lacrimal and salivary glands, the mammae, and the intestinal mucosa seem to be able to keep the pigment from passing out with their secretions. The ocular fluids are colored.

The pigment in solution saturates the tissues. The granular pigments, yellow, brown, or greenish in color, may be seen in the cells or in the interstitial tissues; the crystals, yellow or red in color, are usually extracellular. The pigment displays the spectral play of colors on contact with strong nitric acid, and is turned green by weak tincture of iodine.

A special form of deposition is the bilirubin infarct in the urinary tubules. These are seen in severe jaundice of the newborn, but may occur in deep icterus of adults, as in acute yellow atrophy.

Metabolic Pigmentation

The pigmentation derived from cellular activity may be properly termed "metabolic." We know isolated facts about the different forms, but there is little systematic fundamental knowledge. Two facts, however, seem clear: that these pigments are formed by migratory and resident pigment-building cells, which with leukocytes and plasma cells

accomplish the transportation and deposition of the pigments; and that hemoglobin is in some way or other the raw material for their manufacture; some authors, however, think that protein under the influence of ferments produces these metabolic pigments, of which *melanin* is an example.

The manifestations may be local or general. Among the former are the pigmentations of nevi and moles, of pregnancy, of the corpus luteum, freckles, some scars, certain skin diseases, as chloasma and xanthelasma, of the lesions secondary to some cutaneous parasites, etc. A special local type is that seen in tumors, notably in melanosarcomata. Lipomata and sarcomata (chloromata) may be analogously affected.

Among the general pigmentations are those of Addison's disease, of certain severe anemias and cachexias, of tuberculosis of the peritoneum, intestines, and retroperitoneal glands, of abdominal neoplasms, and of senility. The cases associated with abdominal lesions are held to be connected with disturbances of the adrenal bodies or of the chromaffin system, which has been considered to have control of pigment formations.

Oöchronosis is a black pigmentation of cartilage and related tissues, sometimes including fibrous tissues, and on occasion associated with melanuria. It probably belongs with the metabolic pigmentations.

The metabolic pigments are very varied, and a detailed discussion of them here would be unprofitable. They may have a high percentage of sulphur and may or may not contain iron. They are commonly deposited in and between the cells as granules, but may be crystalline. They do not give a play of colors with nitric acid, and have varying solubility.

NECROSIS

Definition.—Necrosis may be defined as the death of tissues. The death of individual cells is termed *necrobiosis*; death of tissue *en masse*, usually accompanied by putrefactive changes, constitutes *gangrene*.

Etiology.—All classes of cellular death may be brought under four etiological groups: 1, those due to nutritional and circulatory disturbances; 2, those due to trophic disturbances; 3, those due to poisons—animal, vegetable, bacterial, and inorganic; and, 4, those due to traumatism, employing the term in its broadest sense. It has been attempted, without success in our opinion, to class the trophic necroses as identical with those due to circulatory and nutritional disturbances; similarly, the poisons and traumatism have been considered as acting only through the circulatory and nutritional paths, but it seems evident that in the light of our present knowledge the four groups are to a greater or less degree distinct.

The various causes do not produce constant types of necrosis, but occasion one form in some cases, another in other cases. Prominent among these varying circumstances are the native health of the tissues and their vital resistance, the circulatory relations of the part

involved, the activity and duration of the causal agents, the age of the subject, the presence of other diseases, the temperature of the tissues, etc. It will, therefore, be better first to consider collectively the causes of necrosis, and subsequently detail the varieties of it. There can be no doubt, however, that in the direct forms of necrosis the results are to a marked extent individual to the agent; for example, cells killed by the action of acids, alkalies, and metallic salts present appearances quite characteristic of each.

Circulatory Derangements.—The circulatory disturbances include many conditions. Acute and chronic ischemia, however produced—by embolism, thrombosis, arteriosclerosis and atheroma, by extra-arterial pressure, by cardiac weakness or by arterial spasm, as in Raynaud's disease and perhaps in ergotism—are important conditions. Venous stagnations are responsible for many instances. Actual stasis due to mechanical obstructions and such poisonings as produce coagulations is a rare cause. Heat and cold act partly by circulatory disturbances. Among the general disorders of circulation and nutrition may be mentioned the anemias, the cachexias, senility, and certain metabolic diseases, such as diabetes. In these conditions there is much probability that poisoning by metabolic products plays an important part.

Trophic Derangements.—Forms of necrosis due to trophic disturbances are well illustrated by bed-sores (decubitus), myelitic cystitis, the ulcerations seen in trigeminal neuritis, and the arthropathies. These forms of cell death cannot be brought under the circulatory, toxic, or traumatic classification. They can be explained only by the assumption that the biological mechanism of the cell is disturbed, and that in consequence death occurs.

Intoxications.—The group due to poisons is very extensive and the particular subdivisions numerous. The toxins of bacteria furnish many examples of direct necrosis, and act indirectly in cases which seem circulatory or traumatic, though they are not really so, since these factors only lower the resistance of tissues, which then become susceptible to bacterial action. Experimentally the most exquisite forms of cell degenerations and necrosis can be produced by the injection of toxins or analogous substances like ricin and abrin. The alkaloids possess marked power in the production of necrosis. Acids, alkalies, metallic salts, and innumerable other chemical substances may produce direct necrosis, or indirect necrosis by the preliminary production of degenerations. The same substances often cause both circulatory and mechanical disturbances, which augment their direct effects. Heat and cold act like chemicals; heat alters the properties of proteins; cold affects the fluids rather than the protoplasmic substances; both also induce marked circulatory disturbances.

Mechanical Agents.—The mechanical causes of necrosis are many and varied. Pressure *per se* may cause the death of cells, but is often aided by the circulatory disturbances which it occasions. That tension causes necrosis is an old surgical truth, well illustrated by the results

of collections of exudates below the periosteum and by the results of strangulations. The pressure of calculi, concretions, enteroliths, and exostoses may cause important necrotic processes. Circulatory disturbances often are a very active factor—indeed, many forms of traumatism act solely through them.

Inflammation, whatever its original inception, may become so extreme as to lead to necrosis. Necrosis, on the other hand, often leads to inflammation, the dead cells constituting the primary irritants.

All forms of necrosis are accompanied to a greater or less extent by the various degenerations. In particular the cellular alterations are constantly present, and constitute the evidences of morbid action. The changes are due to disturbances of cell chemistry, among which enzyme action is, of course, the most important. (Reference will be made below to the cellular changes.)

There are several general forms of necrosis which, however produced, have a sufficiently distinct character to warrant separate descriptions. They are coagulation necrosis, liquefaction necrosis, caseation, fat necrosis, hemolysis, and gangrene.

COAGULATION NECROSIS

Definition.—This is defined as that form of death of tissue in which the protein suffers a change similar to or identical with coagulation. It is seen only in those tissues which are rich in proteins, and possibly is due to coagulation of some of these by ferments set free by cell necrosis. The process is partly at least a species of fibrin formation, and is allied to hyaline degeneration. It may be chemically distinct from the coagulation of inflammatory exudate, as fibrin is not always demonstrable. Physically the two are almost exactly the same.

Etiology.—The causes of this condition are those above detailed for necrosis in general. Circulatory disturbances, except thrombosis or infarctions, play a minor rôle here. Chemical irritants and high temperatures frequently produce it. Bacterial poisons are very prone to produce it, especially those elaborated by the pyogenic bacteria, the tubercle bacillus, and the diphtheria bacillus. About every abscess is found more or less coagulation necrosis; it is one of the early changes in tubercles and the fundamental element in the production of pseudomembranes. All exudates and transudates are liable to coagulation.

The serous and mucous membranes are most susceptible; next the muscular tissues (often the myocardium).

Pathological Anatomy.—The tissue has a glazed, opaque, waxy appearance, and is firmer and paler than normal. In later stages the color becomes gray and the tissue inclines to soften. Microscopically it is seen that there is an exudate which has been fixed in the tissues; fibrin is seen (with suitable stains) in the form of granules and fibrils. In addition to the fibrin there is more or less homogeneous matter (fibrinoid) which does not react to stains like fibrin, but which is nevertheless closely allied to that substance. The cells soon lose their elec-

tion for stains (Fig. 24). Early in the process the nuclei may stain faintly and present a homogeneous appearance; later the cell disintegrates completely (Fig. 25). In muscles the striations disappear; and in the cardiac muscle the intercellular cement substance seems to be dissolved,

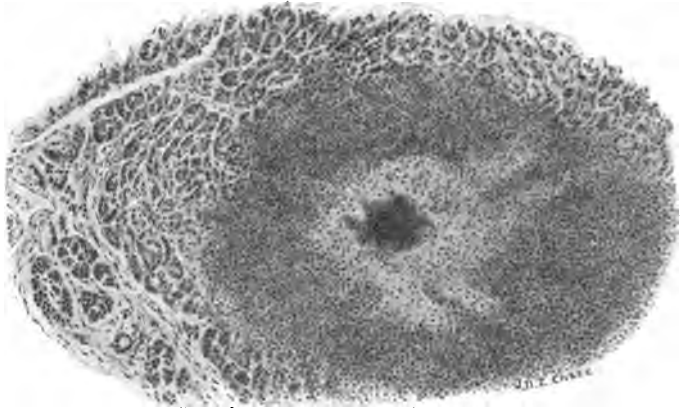


Fig. 24.—Embolic abscess of the pancreas. The darker area in the center represents closely packed staphylococci, filling a blood-vessel and invading the surrounding tissues. The light area around this represents cellular necrosis. The peripheral darker zone shows abundant invasion of leukocytes. The extreme periphery of the illustration shows pancreatic tissue little altered.

for the cells often lie separated and present vacuolation and fragmentation. Pus, leukocytes, and red blood-cells in the affected areas all suffer the fate of the fixed tissue. The blood-vessels at the margin of the area are seen to be thrombosed. In the kidneys the tubules may contain firm casts.

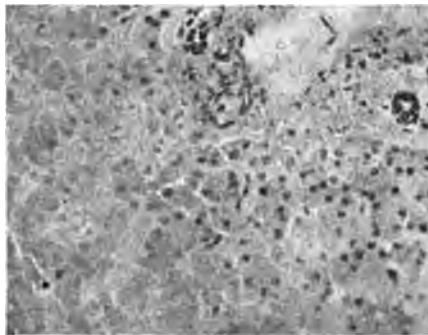


Fig. 25.—Coagulation necrosis of the hepatic cells in a case of puerperal eclampsia (Karg and Schmorl).

Morbid Physiology.—Many chemicals cause coagulation by direct action. In the larger number of instances, however, it must be assumed that the fibrinogenetic substances which bring about the coagulation of the proteins are derived from the necrobiotic cells in the area or are carried thither by the lymphatic cells. There is consid-

erable evidence that bacterial products may act fibrinogenetically. It has been contended that coagulation necrosis is simply a species of inspissation of the tissues. This is certainly not the case.

An area of coagulation may be cast off by the process of ulceration, may undergo liquefaction, caseation, or suppuration, may be encysted, and apparently may be dissolved and reabsorbed. The area of disease may finally be converted into scar-tissue by secondary regeneration. More or less complete loss of function results from this form of necrosis.

LIQUEFACTION NECROSIS

Definition.—This change consists in the death of tissue with colliquation. It may be divided into primary and secondary forms. Secondary liquefaction necrosis is the form in which other varieties of necrosis or degeneration are followed by liquefaction. Thus, areas of coagulation necrosis, cheesy necrosis, and of inflammation, gangrenous tissue, and tumors may become liquefied.

Among the special forms may be mentioned vesicle formation and the softening of caseous tuberculous lesions. A very frequent seat of liquefaction necrosis is the central nervous system, where the conditions are unfavorable to coagulation, so that liquefaction here follows pathological conditions which would elsewhere produce coagulation. Circulatory disturbances, traumatism, and intoxications all cause softening in the central nervous system; the peripheral nerves are much less susceptible.

Pathological Anatomy.—In the early stages the tissue is softer than normal and very rich in fluid. Later, when the solution of the fibrillar tissues is advanced, the area becomes filled with a liquid of greater or less consistency, depending upon the tissue involved. The cells in the area are seen in all stages of degeneration; later, nothing but detritus is visible. In some instances, instead of becoming more and more fluid, the exudate undergoes coagulation. The color may be white, from the presence of an emulsion of fats; yellow, from fats and pigments; red and brown, from the presence of blood-pigment; and deeply colored when jaundice is associated.

The process consists in the infiltration of fluid into tissues and the more or less complete solution of the tissue elements in it. It has been compared to the alterations of proteins by digestion—a reasonable deduction, since the solution of the tissue or infiltrate occurs by digestive ferments. Should the process be of bacterial origin, the enzymes of the organisms are added to those of the infiltrative cells. Should bacteria be absent, the ferments are freed chiefly after disintegration of the cells. (See Autolysis.)

Areas of liquefaction may discharge their contents, may coagulate, may be reabsorbed, encysted, or, in uncommon instances, organized.

CASEATION

This is the crude name applied to a complex process whose product has a cheese-like appearance.

The condition is most frequently seen in connection with tuberculosis, although it is found in the other granulomata, and also in other pathological processes. The preliminary *conditio sine qua non* of caseation is coagulation necrosis. The modern view of the origin of caseation seems to be that it is a failure of an infiltrate to undergo complete liquefaction necrosis because the enzyme-bearing leukocytes are not attracted, and such enzymes as may be present are inhibited by the unsaturated fatty acids of the tubercle bacilli. Anemia of caseous areas, tuberculous or other kinds, plays a large part in the incomplete softening. Caseous matter is composed of coagulated protein and fatty matter. Secondary infection brings blood-serum, which dilutes the enzyme-inhibiting soaps.

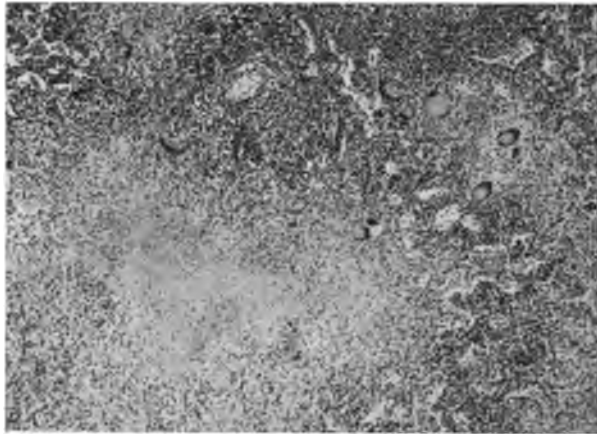


Fig. 26.—Large tubercle of the lung, showing cheesy necrosis.

The early tubercle, before the occurrence of softening, has an appearance like that of cheese, but is less homogeneous and more granular (Fig. 26). A form of caseation quite similar in appearance occurs in pneumonia, in tumors, and especially in syphilis. Soft caseation is usually coagulation necrosis advanced to liquefaction, together with fatty metamorphosis, so that the appearances are those of soft, creamy cheese. The liquefaction necrosis of the central nervous system may present similar appearances.

Microscopically, the tissues in caseation show no cells preserving their staining reactions; everything is converted into debris. Around the affected area is usually found a zone of coagulation, of inflammation, or both.

Tissues that have undergone caseation may be cast off, reabsorbed, or encysted; resolution is not possible. Calcification is a frequent termination.

FAT NECROSIS

This term is now used to designate a peculiar type of necrosis to which the fatty tissues are subject, and is distinct from ordinary fatty metamorphosis. In human beings it is seen almost exclusively in the abdomen, abdominal walls, and subperitoneal fat. In nearly all instances it appears in connection with pancreatic disease—cysts, tumors, obstruction to the duct, and the various forms of acute pancreatitis. In rare instances the pancreas has not seemed especially diseased. In one case known to one of us of hypertrophic cirrhosis of the liver the omentum was affected, while the pancreas showed nothing but a moderate degree of fibrosis.

The affected areas are white in color, usually not larger than a pea; they may be soft or quite gritty. Inflammatory reaction may or may not surround them. On microscopical examination crystals of the fatty acids may be seen, together with more abundant crystals of a combination of lime with the fatty acids. This combination, it appears, is not a primary feature in the necrosis, suggesting that the fatty acids are first set free and then unite with lime-salts. In experimental work by Hildebrand, Williams, and Flexner it seems to have been shown that the typical condition may be the result of direct action of the fat-splitting ferment of the pancreatic secretion. It is certain, however, that in some cases of pancreatic cysts containing steapsin no fat necrosis has occurred. Bacteria have been supposed by some to be the essential agents causing the change, but this has not been demonstrated.

H. Gideon Wells, after quite extensive experiments on animals, states that fat necrosis is merely a special form of necrosis of fat tissue, differing from the simple necrosis chiefly in the sharp limitation of the affected area, usually by a wall of leukocytes and later by connective tissue, and the filling of the necrosed cells by the products of fat splitting.

It seems to be due to the action of one of the ferments of the pancreatic juice, most probably lipase (steapsin). As this ferment cannot be isolated, absolute proof is wanting. It may be that the lipase causes the fat splitting after some other ingredient of the pancreatic secretion has injured the cell.

The digestive enzyme is supposed to reach the fatty tissues of the abdomen by weakness of the pancreatic duct wall or pancreas capsule due to obstruction or inflammation. In such a condition bacteria may also escape and assist in the fat necrosis. Entrance of bile or intestinal contents into the pancreatic duct is said to favor the production of fat necrosis.

Lipase acting on the fat cells splits up their contained fat into glycerin and fatty acids. Glycerin diffuses, leaving behind the fatty acids. The cells become necrotic and eventually the fatty acids combine with calcium salts and are precipitated, while a new growth of connective tissue encapsulates the area and diminishes its size.

Dissemination of fat necrosis outside of the abdominal cavity has been observed as early as twelve hours after intraperitoneal injection in animals, the route of spreading being probably by the lymphatics.

The suggestion made at one time that bacteria might be the cause of fat necrosis has been entirely given up at the present time.

Focal Necroses.—This is a condition of multiple small necroses in areas barely visible to the naked eye or discoverable microscopically. They occur in all parenchymatous organs and glands. The chief causes are vegetable toxins. In the small areas the nuclei first lose their staining reactions, the cytoplasm later. There occurs an influx of leukocytes, giving the appearance of an early abscess. These necroses are accounted for in two ways: bacteria or their products may be present directly in the foci, or the necroses may be due to obstruction of capillaries. The obstruction may be embolic or, as Pearce suggests, in the nature of a thrombosis due to hemolysis with collection of erythrocyte debris.

Hemolysis, or blood destruction, is a term limited to the red cells, and indicates destruction of the cell with dispersion of its hemoglobin. (The causes and other features are described under Pigmentation and Diseases of the Blood.)

GANGRENE

Definition.—Gangrene, formerly defined as the death of tissue *en masse*, is perhaps best defined as the putrefaction of areas of necrosis. It may be *primary*, when a particular bacterium produces a gangrenous inflammation as its direct result, as in malignant edema; or *secondary*, when saprophytic bacteria decompose an area already necrosed from other causes. It may be *dry* or *moist*, according to the location and supply of fluids. It may, furthermore, be *circumscribed*, *progressive*, or *metastatic*.

Primary gangrene constitutes a specific affection or, rather, a number of specific affections. Malignant edema, infectious emphysema, and some forms of anthrax may be included in this group. In these conditions there is violent infective inflammation, with practically immediate gangrene of the affected parts.

Secondary gangrene is more common, and the appearances are very varied. The essential condition is putrefaction of a necrosed area.

Dry gangrene is usually due to vascular disturbances. As a result of arterial obstruction it is seen in the extremities in senility, and following arterial embolism or thrombosis of whatsoever nature if the collateral circulation be insufficient to nourish the part. Freezing may produce a dry form of gangrene, the vessels being blocked by thrombosis. Ergotism causes dry gangrene as a rule; the same may be said of Raynaud's disease. Finally, dry gangrene may result from the moist form, when putrefaction is slow and evaporation of the fluids occurs. The putrefactive processes in the dry type are not marked and may cease entirely. Dry gangrene is generally circumscribed and the end-result of a typical case is *mummification*. The color is usually dark, finally black; early

it may be yellow or brown; rarely the tissues are very pale. There is little toxic absorption in these cases.

Moist gangrene presents numerous varieties. It is rarely produced by arterial occlusion, but is the usual result of extensive venous occlusion. Internal emboli, as in the pulmonary arteries or veins or mesenteric arteries, not infrequently cause gangrene of this form. It also occurs in the lungs as a result of inspirational or other pneumonias, abscess, neoplasms, bronchiectasis, and in diabetes. It is seen as a result of traumatism and pressure in severe contusions (especially with vascular injuries), in intussusception and strangulation of the bowel; as a result of torsion in movable kidneys, spleens, or tumors. It is frequent in the obstructed or strangulated vermiform appendix. Extensive moist gangrene of the extremities or other parts is not rare in connection with diabetes. The mucous membranes may become gangrenous as a result of various infections. A particular form is noma of the mouth and genitalia. It is seen as a rare condition in certain skin diseases; and is not unusual in severe trophic lesions, as decubitus, cystitis, mal perforans, etc.

In moist gangrene the consistency of the part becomes progressively softer. There may be local or widespread emphysema. The color is usually dark brown, due to disorganized blood-pigment; the skin commonly becomes black and is covered with blebs. About the area there may be a zone of coagulation necrosis with vascular thrombosis, or a zone of inflammatory reaction which will produce a line of demarcation. In some cases, especially the diabetic, neither of these zones is formed.

The cells first succumb. The protoplasm and nuclei exhibit various evidences of degeneration, the nuclei disappearing and the cells becoming converted into granular detritus. Fat and the myelin-sheaths of nerve-fibers are reduced to free fat and fatty crystals. The muscle cells lose their striations and become fragmented; the axis-cylinders of nerves fibrillate. Hemorrhages into the area are common, due either to erosion of vessels and expulsion of their thrombi by the pressure of the blood-current, or to a genuine hemorrhagic condition the result of toxemia. Connective tissue and elastic fibers resist longer than the cells, but finally become liquefied. The affected area contains crystals of pigment, fatty acids, cholesterin, leucin, tyrosin, phosphates, and carbonates. Ammonia, the fatty acids, indol and skatol, sulphuretted hydrogen, carbonic acid and other gases, usually of pronounced odor, are formed. There is more or less toxic absorption from these areas.

But two things can happen to an area of gangrene: it may progress and cause the death of the individual, or may become circumscribed. In dry gangrene and in the vascular forms of moist gangrene, limitation is the rule; the other moist forms tend to be progressive. In the circumscribed form a line of demarcation is formed by inflammatory reaction, and the mass is finally cast off as a *sphacelus* or slough if the area be superficial, or encysted if the area be internal. The latter cases may be followed by reabsorption of the contents and calcification of the sac.

GENERAL PATHOLOGY OF CELLULAR NECROSIS

The cell as an individual element is liable to pathological processes of various kinds that merit brief consideration, apart from definite forms of tissue degeneration and necrosis.

Etiology.—The causes of cellular degeneration and necrosis are numerous, including mechanical, thermal, electrical, chemical, and vital (trophic) influences of various kinds. It is easy to demonstrate the influence of some of these causes in the unicellular organisms, such as amebæ, and the changes thus produced may also be seen under proper conditions in the cells of the animal body.

Pathological Anatomy.—The cell as a whole may show various forms of distortion, or internal change. Increased irritability and mobility of the protoplasm cause the projection of pseudopodia, and these may be separated from the body of the cell as rounded particles more or less resembling the original cell. This is easily demonstrable in red blood-corpuscles subjected to heat. Sometimes particles are discharged from the cell and vacuolations (expulsion vacuoles) result. Certain influences, like cold and metallic salts or other poisons, cause a reduced mobility and general contraction of the cell.

ALTERATIONS IN CELL NUCLEI IN NECROSIS

1. Karyorrhexis.
 - a. Degeneration of the Cell Membrane (Chromatolysis).
 - b. Budding of the Cell Membrane.
 - c. Pyknosis.
- a. Degeneration of the cell membrane is a regular phenomenon of gradual physiological cell destruction, as in the ovary, testis, epithelia, etc. The membrane thickens (hyperchromatosis) and shows clumped areas.
- b. In the budding process the nucleus may be small and deeply and homogeneously stained and surrounded by small spherical, bud-like projections, or there may be very large club-like projections which extend to the periphery of the cell or even outside the cell.
- c. The pyknotic nucleus is smaller than normal, deeply staining and homogeneous in character. Contraction of the nucleus leaves a vacant zone about it, so that it seems to lie in a vacuole.

2. Karyolysis.

The nucleus undergoes a gradual solution, but its size and shape may still be recognized by the delimitation of the surrounding protoplasm even after complete solution.

This, in contradistinction to the various types of karyorrhexis, is essentially a postmortem change and occurs when dead cells are still surrounded by tissue fluids.

ALTERATIONS IN THE FORM OF CELLS IN NECROSIS

In association with pyknosis of the nucleus the cells shrink and become jagged. In conditions in which there is fluid surrounding necrotic cells, the cells at first swell and later contract. Various irregularities of shape may occur.

Among the various forms of degenerative change in the cell preceding its necrosis are vacuolization, cloudy swelling, and dropsical degeneration, loss of pre-existing granules or granulation of previously homogeneous protoplasm, pigmentation, and hyaline and glycogenic change. These degenerations may affect only part of the cell, the surrounding protoplasm remaining healthy. In such cases the appearance of alien inclusions is given, and such areas of degeneration have frequently been mistaken for animal parasites. Russell's fuchsin bodies are examples of this condition.

Among the changes observed, alterations in the Altmann granules, which occur in many cells, are significant. These granules first become larger and more readily

demonstrable, their affinity for acid anilin stains increasing. These changes are variously ascribed to increase of acid radicals from protein cleavage in autolysis, to precipitation of colloids, and to condensation of colloids by pressure when the endosmosis of water and solids is greater than the exosmosis of metabolic products. The changes are exemplified in the cellular degenerations known as cloudy swelling and hydropic degeneration.

Certain methods, such as hardening in a mixture of 2 per cent. osmic acid solution and 5 per cent. potassium bichromate solution, staining in hot 20 per cent. anilin-oil acid-fuchsin solution, differentiation with alcohol, picric acid solution, are necessary to demonstrate the granules. In the degenerated cell even the fresh tissue or that hardened in alcohol or formol and stained with acid anilin suffices.

Next the granules lose their characteristic arrangement; they partly dissolve and partly aggregate in large spherical masses which may be extruded from the cells.

In the third stage there is an altered chemical composition evidenced by changed staining affinity. The granules without special preparation of the tissue, may be stained with Weigert's fibrin method, or they may lose their staining capacity, or in the third place, acidophilic granules may become basophilic or the reverse.

ALTERED KARYOKINESIS IN NECROTIC CELLS

1. The chromosomes may become notably thickened, especially in cases in which injuries are inflicted on cells already dividing.
2. Granular fragmentation and alteration of staining reaction of the chromosomes. The cell itself may be vacuolated. The nuclear fragments become acidophilic.
3. Hypochromatic Mitosis. The number of chromosomes may be reduced to 6 or 8 or to an uneven number, as 7 or 5. Such changes are seen in rapidly growing malignant tumors and in rapidly regenerating tissue acted upon by destructive agencies.
4. Broken Chromosomes. Parts of chromosomes broken off from the main body are scattered about in the cell outside the nuclear spindle. The process seems to be one essentially affecting the achromatic spindle. Thickening, clumping, and oxyphilic change of the chromosomes are associated conditions.

Such changes have been found in cells unfavorably influenced after division was under way.

5. Asymmetrical Mitosis. The daughter stars may have an unequal number of chromosomes and thus be of unequal size.
This has been found in carcinomata, sarcomata, adenomata, and regeneration of the epidermis.
6. Hyperchromatic and Multiple Mitosis.

The number of chromosomes may be excessive and there may be pluripolar mitosis, the number of centrosomes and corresponding spindles being 4-6, 8, and even 20.

POSTMORTEM ALTERATIONS

Certain changes take place after death which may suggest in their appearances antemortem disease. It is, therefore, necessary to recognize these in postmortem examinations. The most striking change is the rigidity or *rigor mortis*, which is due to a coagulation of the muscle albumin or myosin, probably by reason of the lactic acid present. This occurs at different intervals, according to the cause and nature of death. Sometimes, as in deaths after electrical discharges, it occurs almost instantaneously; more commonly its beginning is delayed for some hours. It appears early in cases dying with active muscle metabolism, and late in wasting diseases. After twenty-four or forty-eight hours the rigidity disappears. Occasionally irregular postmortem contractions of the muscles take place, and distortions or even movements are thus produced.

Circulatory Phenomena.—As is noted elsewhere (see Congestion), the blood-vessels, especially the arteries, contract after death, and drive the blood into the capillaries and veins. It is then more or less free to sink to dependent parts through the influence of gravity, and in consequence the lower parts of the organs and of the body in general are congested. This is particularly marked in the lungs, but occurs in practically all organs. The blood may remain entirely within the blood-vessels, but not rarely the coloring-matter diffuses itself through the tissues and causes pigmented areas (*livores mortis*) that may suggest antemortem bruises.

The blood in the heart and other vessels tends to coagulate, though in some cases this is long delayed and remains imperfect. Usually dark red clots are found in the cavities of the heart and in the large vessels. Yellowish fibrinous clots are less likely to be postmortem, but more often occur in cases in which death has taken a lingering form.

Postmortem Degeneration of Tissues.—Some time after death the tissues may become macerated and putrefactive changes may occur. To a large extent these are due to invasion of micro-organisms. It has been found that during the terminal stages of disease various forms of infection (especially micrococcic) occur. This *terminal infection* is often the immediate cause of death, and it is also concerned in the postmortem change in the tissues. Histologically, a striking peculiarity of such postmortem change is the absence of evidences of reaction (cellular infiltration and proliferation), such as characterize the response of living tissues to irritation.

Postmortem softening of the mucous membranes may be due to the action of the secretions. This is especially marked in the stomach, where it is common to observe a macerated condition of the mucosa of the posterior wall. In this case the gastric juice is the direct cause of the alteration in the mucous membrane.

Autolysis.—After death, either local or general, tissues tend to soften, the process being due to intracellular enzymes in the absence of bacteria. The activity of these ferments is held in check during life by the antiferment action of blood-plasma. All inhibitive agencies being removed by death, favoring factors appear in the shape of a slightly acid reaction due to overneutralization of tissue alkalinity by acids formed in fermentation and putrefaction. The intracellular enzyme is now freed and digests the cell. This is essentially what occurs in the resorption of pathological processes during life. All cellular enzymes are not identical. The most conspicuous cell ferment is that contained in the wandering leukocytes which acts as a solvent in inflammatory exudates.

CHAPTER V

INFLAMMATION AND REGENERATION

INFLAMMATION

Definition.—Inflammation is the local reaction caused by agents that have produced tissue injury. The essential element in this reaction is fluid and cellular exudation and the attraction to the place of injury of wandering cells. A less essential but almost invariable feature is local hyperemia, while the processes of repair or regeneration usually accompany, but are not strictly a part of, inflammation. By reason of the fact that the term “inflammation” was originally a clinical one and designated *all* the results of local injury, that is, damage, defensive processes, and repair, and further, by reason of the fact that injury and repair naturally go hand in hand in living tissues, it has always been a matter of difficulty for pathologists to determine what part of the processes occurring in an area of inflammation constitute its essence, and what part represents results or consequences. In the present state of knowledge we recognize and can distinctly separate two sets of phenomena following local injury, the first being reactive and defensive; the second, reparative. The latter, while intimately interwoven with the former, do not differ from regenerative processes that are known to occur without inflammation. Viewed in this light the term “inflammation” is restricted to the defensive processes that follow injury, while the repair of damage is a natural sequel manifesting the vital capacity of tissues to restore themselves.

There are certain other *consequences* of inflammation that are sometimes included among its essential phenomena. Thus, certain pathologists insist that inflammation is general, not merely local; that the whole body participates in certain ways. There can be no doubt that the irritants causing inflammation as well as products of tissue destruction do gain access to the circulation to some extent, and thus occasion general results throughout the body, and it is also true that widespread co-operation may be induced through the action of the nervous system. These are results or sequels of inflammation, but not an essential part of the condition. When the local defensive mechanisms occurring in inflammation (let us assume, of bacterial origin) are inadequate, the micro-organisms may gain access to the general circulation and general “infection” result; when products of tissue destruction similarly escape into the general circulation an “intoxication” results. Neither of these is an essential part of inflammation, but rather the evidence that this process has been inadequate to fulfil its purposes. Such coöperation of the whole body as may be induced through the nervous

system is reactive and is similar to that which must of necessity attend any local disease. It, too, is a consequence, but not an essential part, of inflammation.

For purposes of description, however, it is better to include in the chapter on inflammation the regenerative processes that accompany it, and also some account of the general reactions of the whole body. Regeneration independent of inflammation, or with but slight evidences of preceding inflammation, will be separately considered later.

Historical.—The earliest conception of inflammation was that of a specific entity. Subsequently various theories were offered in explanation of the several phenomena or symptoms. First, the blood-vessels were supposed to be influenced through the nervous system (*vascular theories*). Next, it was taught that the inflammatory irritant excites proliferative changes in the tissues (thus giving rise to round cells), and that this stimulation of the cellular activity invites more blood to the part (hence the hyperemia). This was the *cellular and attraction theory* of Virchow. Others, notably Cohnheim, described the emigration of leukocytes from the blood-vessels, and held this to be the essential feature of inflammation. This emigration was first described by Dutrochet (1824), Waller (1842), and Stricker; but Cohnheim was the first to systematize the *emigration theory*. According to Virchow, the first step is a formative stimulation of the cells; according to Cohnheim, degeneration of the vessels leading to emigration; according to Weigert, at least in many cases, the first step is necrosis of the parenchymatous cells. Metchnikoff and his students would elevate phagocytosis to the position of the essential feature of inflammation, but the prevailing opinion is that reactive tissue changes and enzyme activity are equally important, both within and without the cell.

Galen and his followers defined inflammation by giving the cardinal symptoms: heat (*calor*), redness (*rubor*), pain (*dolor*), and swelling (*tumor*). To these may be added altered function (*functio læsa*).

Phenomena of Inflammation in Vascular Tissues.—These may be well studied in the mesentery or tongue of a frog. When the mesentery is exposed and spread under a microscope and a localized area injured, the first visible effect is a very temporary contraction of the arteries, which may disappear before the examination can be made. It is followed by dilatation of the arteries, and then of the capillaries and veins. The tissue becomes distinctly more vascular than normal as capillaries in which there had been only plasma or a few corpuscles become distended with blood, and, therefore, more distinct. The blood-current is at first more rapid than normal, then slower, and may finally stop entirely (stasis), especially in the capillaries and veins in the center of the inflamed area. Notable changes are seen in the circulating corpuscles. It will be recalled that under normal conditions the corpuscles circulate in the middle of the vascular stream, leaving a clear plasmatic zone adjacent to the vessel wall; in this zone may be seen leukocytes traveling somewhat more slowly than the central corpuscular stream. As the current becomes slower the leukocytes in the plasmatic zone increase in number and stick to the vessel walls, at first here and there, holding on uncertainly, but finally becoming more firmly attached and arranging themselves in a continuous row. In the capillaries clumps of leukocytes frequently alternate with masses of red corpuscles, or of

red and white corpuscles in their customary proportion. Next, it may be observed that the leukocytes are passing through the walls of the capillaries and veins and spreading in the outside tissues. At first a bud-like projection pushes itself through the vessel wall, then more and more follows until the whole leukocyte has escaped into the tissue space outside the vessel. At the same time a certain number of red corpuscles pass through the capillary walls, and altered plasma escapes and infiltrates the tissues. Some of the leukocytes enter the lymph-channels and thus return to the circulation; others suffer degeneration and destruction locally.

In the perivascular tissue the emigrated leukocytes are found in tissue spaces and tend to accumulate where the injury is greatest. If there be a large area of destruction, these cells surround it. The leukocytes soon exhibit their phagocytic power by enclosing bacteria, fragments of dead cells, and debris. The enclosed parts are dissolved by the intracellular ferments and are soon unrecognizable. Some of the phagocytes are themselves destroyed in this attempt to remove invading bacteria and degenerated cells; and becoming, in turn, degenerated, break down into a debris upon which other phagocytes feed. There appear within the cellular exudate also large mononuclear phagocytic cells with large palely staining nuclei, the so-called macrophages. These take up all kinds of debris or even whole leukocytes and red blood-cells. Their origin and functions will be considered later.

While this is going on, reparative processes appear in the shape of round newly formed connective-tissue cells which alter their form to spindle or irregular contour, and finally produce fibrillar projections. These are fibroblasts, the principal regenerative cells.

In structures in which there are parenchymatous (archiblastic) cells the latter undergo various degenerative changes, such as cloudy swelling, edema, mucous degeneration, fatty degeneration, or even necrosis. Less frequently proliferation of the parenchymatous cells takes place.

Every case of inflammation does not present all these phenomena, nor is the subsequent fate of the exudate and altered cells always the same.

Phenomena of Inflammation in Avascular Tissues.—Some of the processes of inflammation have been best elucidated by experimental inflammation of the cornea. It will be recalled that this structure is composed of layers of parallel fibers, the direction of the fibers in one layer being at angles to that of the fibers of adjacent layers. Anastomosing lymph-channels occupy the spaces between the fibers and layers, but there are no blood-vessels. A very slight injury of the cornea may be followed by no other result than slight swelling of the corneal corpuscles around the point of injury and subsequently multiplication of these cells to repair the damage. This slight change cannot be readily demonstrated. Usually there is seen around the injured spot a hazy zone which is composed of masses of leukocytes that have been attracted to the center of irritation. These escape from the hyperemic conjunctival vessels at the periphery of the cornea. The alteration

(dilatation, degeneration of the walls) of these vessels may be due in part to reflex nervous influences, and in part to the direct action of toxic substances generated at the site of the primary corneal injury and diffused to the surrounding tissues.

The corneal corpuscles themselves swell, undergo nuclear division, and to some extent perhaps become free (phagocytic) cells. In more intense grades of inflammation the local degeneration of the corneal corpuscles causes a visible defect (erosion, ulcer), and the surrounding zone of leukocytic invasion is pronounced. In cases of marked corneal inflammation new blood-vessels are later formed at the sides of the cornea, and pushed into its previously avascular structure; the subsequent phenomena are practically the same as those found in inflammation of vascular tissues.

In the case of inflammation of the heart-valves no migration of leukocytes to the diseased focus occurs in the early stages. The endothelial cells at the point of injury (near the free edge of the valve) swell and present nuclear division and also more or less degenerative change; the tissues at the base of the leaflets become hyperemic and some emigration of leukocytes occurs in this situation. Thus, as in the case of the cornea, cellular destruction and proliferation occur at one place (the point of injury), while the vascular phenomena and emigration of leukocytes are found at some distance. In both cases there may eventually be an ingrowth of loops of capillary blood-vessels from the vascular periphery into the avascular structure, and then local emigration of leukocytes from these capillaries may take place.

The phenomena must now be separately considered.

1. Changes in the Vessels.—The first effect of irritation may be momentary contraction of the arteries; but this is rarely observed. Usually the arteries dilate at once, and dilatation of the capillaries and veins promptly follows. This is at first a regular or uniform distention, but shortly becomes irregular, causing inequality of caliber and tortuosity. The cause of this dilatation was formerly located in the nervous system, and undoubtedly nervous influences do play a part in some cases at least, but the more important cause is probably some degeneration of the vessel walls. The primary dilatation may be due to the direct effects of the toxic agent causing the inflammation or to products of cell degeneration it has occasioned. It may be purely functional at first, but later is surely degenerative. The microscope does not reveal this, but some of the phenomena connected with exudation and the circulation of the blood show that there is some lesion of the vessel walls. There are certain visible changes in the vessels, such as swelling of the endothelial cells and increase of the intercellular substance, and some undoubted though invisible changes, such as increased adhesiveness of the endothelial cells. The last-mentioned condition and the swelling of the endothelial cells which thus encroach upon the lumen of the vessels are conditions that, together with the dilatation of the blood-vessels, occasion slowing of the blood-current and adhesion of the leukocytes to the vessel wall.

In the later stages of inflammation karyokinetic changes and consequent multiplication of the endothelial cells of the capillaries are observed. The new-formed endothelial cells are utilized in the production of new blood-vessels. (See Granulation Tissue.)

Influence of the Nervous System.—It is likely that the nervous system through its vasomotor mechanism plays an important rôle both centrally and peripherally in the vascular and exudative phenomena of inflammation. Dilatation of the vessels may be favored by weakness of the constrictors or stimulation of the dilators. This is illustrated by the severe inflammations resulting from trivial causes in paralytic parts, and by the occurrence of sympathetic inflammation in one eye following disease of the other. In the latter instance the trophic nerves are also concerned.

2. **Exudation.**—As the blood-current grows slower the leukocytes in the plasmatic zone of the blood-stream increase in number and cling to the wall of the vessel. This is partly a mechanical result of the

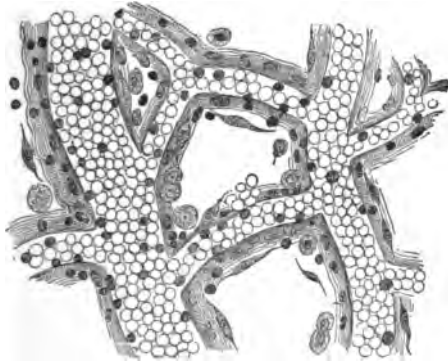


Fig. 27.—Inflammation of the mesentery, showing overfilling of the blood-vessels, with emigration of leukocytes and diapedesis of red corpuscles (Ziegler).

slower rate of the blood-current, and partly the result of the adhesiveness of the vessel walls and projection of the endothelial cells. Possibly the attractive (chemotactic) influence of the agents causing the inflammation may play some part by drawing the leukocytes to the walls of the vessels (see below). Finally, the leukocytes pass through the vessel walls between the endothelial cells and collect on the outside of the blood-vessel, whence they more slowly migrate through the tissue (Fig. 27). The passage of the leukocytes through the vessel wall can be studied in the mesentery of the frog. At first a bud-like projection pushes itself through the wall between the endothelial cells, then more and more of the corpuscle follows until the whole cell has escaped. When outside the blood-vessel the cell creeps through the tissues in the intercellular spaces, often elongating itself in narrow places to a linear form, and again swelling to its normal rounded form where fluid exudate has widened the spaces. This emigration of leukocytes occurs to a slight extent normally, but is abnormal in degree in inflammation. Cohn-

heim ascribed it to disease of the vessels—increased permeability—the leukocytes being purely passive. Later observation indicates that the chief rôle in this excessive emigration must be assigned to the stimulated ameboid movements of the leukocytes. Degeneration of the vessel walls, especially swelling and softening of the cement substance between the endothelial cells, and the pressure of the blood, aid, but only to a minor extent. The cause of this active ameboid motion and tendency to emigration has recently been found to be an attractive force peculiar to the causes of inflammation. Stahl, and later Pfeffer, found that certain substances exert an attractive or repellent force upon low forms of vegetable and animal life, upon spores of plants, and upon bacteria. To this force the name *chemotaxis* has been given, and the terms *positive* and *negative chemotaxis* are used to designate the attraction and the repulsion respectively. The irritant substances which directly cause inflammation are positively chemotactic in action; and in cases in which mechanical injury causes inflammation, such substances first result from mechanical destruction of cells and then incite the subsequent phenomena of inflammation. The leukocytes that emigrate under the influence of a chemotactic agent are almost exclusively the polymorphonuclear forms, and these constitute the majority of the cells of an inflammatory exudate in its earlier stages. They are not, however, the only forms of leukocytes found in an inflammatory area. Frequently the first to appear are the eosinophiles. Sometimes these cells are very abundant in the inflamed part. In somewhat later stages lymphocytes also emigrate, and as the polynuclear forms disappear the lymphocytes become more and more predominant. In part these doubtless emigrate from the blood-vessels, but the greater number is derived from the lymph-channels and regional lymphoid collections, for such collections are exceedingly widespread throughout various tissues and organs. The lymphocytes are prone to occur in groups, which has led some authorities to attribute their presence to hyperplasia of existing lymphoid collections, and to some extent to the attraction exerted on the lymphoid cells of the neighboring lymph-spaces toward the existing lymph-nodes in the affected area. While the tendency is to group together, they also increase among the growing fibroblasts, and, as said above, crowd out the polymorphonuclears. Plasma-cells¹ and mast-cells are also found, but as the significance of these is still doubtful,

¹ *Plasma-cells*.—The cell described under this term by Unna is a small cell whose protoplasm stains a violet blue with methylene-blue. There are no distinct granules, though sometimes the protoplasm is slightly granular. The granules have some relation to those in the lymphocyte. This cell is one of the so-called lymphocyte series. The nucleus is usually eccentrically placed and surrounded by dark masses of chromatin. The cell varies in size from that of the small lymphocyte to that of the large mononuclear leukocyte. Karyokinesis has been observed in a few cases. The plasma-cell is probably an altered lymphocyte which has escaped from the blood-vessels. Some hold that it is a form of connective-tissue cell and that it is concerned in regeneration of connective tissue. This is unproved and unlikely. The plasma-cell is found in inflammatory exudates of all sorts and in the lesions of the specific infectious diseases—tuberculosis, leprosy, syphilis, etc.

The plasma-cell of Waldeyer is different from that above described. It is identical with the mast-cell of Ehrlich. This is a cell containing large basophilic granules. (See Diseases of the Blood.) It occurs in inflammatory processes of a chronic character and in various tumors and degenerative lesions. Its significance and nature are uncertain.

separate reference will be made to them below. The plasma-cell undoubtedly plays an important rôle in some cases, as the inflammatory exudate may consist almost wholly of this type of cell.

The microscopical appearance of the tissues after emigration of the leukocytes is characteristic. The capillaries are dilated and obscured by a mantle of exuded white corpuscles, and the tissue around swollen by fluid and infiltrated with migratory leukocytes. The subsequent distribution and appearance of the leukocyte depends very much upon the character of the inflammation and of the tissues in which it occurs.

The changes going on within the cell consist of fatty, cloudy, albuminoid, or dropsical degeneration of organ cells, while hyaline or mucoid metamorphosis is seen in connective-tissue cells.

The cellular character of the exudate varies somewhat with the tissue involved and the nature of the irritant. For example, in the pyogenic infections at the height of the condition one sees almost exclusively polynuclears. In tuberculous inflammations lymphocytes predominate; while in pneumonia, polynuclears and epithelial cells are in greatest numbers.

Diapedesis of Red Corpuscles.—Finally, a certain number of red corpuscles escape from the capillaries by diapedesis. This is a purely passive process so far as the red corpuscles are concerned, being due to pressure of the blood. It is particularly marked when stasis and consequent intravascular thrombosis has occurred. In very intense inflammation accidental hemorrhage *per rhexin* may add to the blood in an exudate.

Rôle and Fate of the Leukocytes.—The most essential element in the defense against the injurious agents that cause inflammation is the emigrated polymorphonuclear leukocyte. This cell possesses a marked capacity to swallow or ingest bacteria or other foreign bodies, which has given the process the name *phagocytosis*, and the cell exercising this function the name *phagocyte*. When bacteria (especially pyogenic micrococci) or small particles of insoluble material, such as carmin or carbon, are introduced into the tissues or into serous cavities, polymorphonuclear leukocytes speedily gather about and incorporate the foreign bodies in their protoplasm. So far as bacteria are concerned, some preliminary action is exerted on them by the blood-serum of the fluid exudate (see below). This is demonstrated by the fact that the polymorphonuclear cells will take up larger numbers of micrococci from a suspension in serum than from one in normal salt solution. The substances which act to prepare the micro-organisms are termed *opsonins* (see p. 258). Possibly *precipitins* and *agglutinins* also aid in some measure. After their ingestion the micro-organisms are either digested within the phagocytic leukocyte and thus disappear, or the phagocyte with its contents enters lymphatic channels and reaches the regional lymphatic nodes. Thus the micro-organisms are disposed of and removed from the center of infection as speedily as possible. Insoluble foreign bodies and products of tissue destruction (fatty globules and

detritus) are also taken up by the phagocytic leukocytes and dissolved or removed to the neighboring lymphatic nodes. In this combat with the foreign invaders a certain number of the leukocytes perish and may be found in various stages of disintegration. Some of them are ingested by other polymorphonuclear leukocytes, but in the later stages of inflammation they are found enclosed in other phagocytic cells of large mononuclear type, which will be described presently.

The various processes described bring about a removal of the microorganisms or other causes of inflammation, and at the same time a steady diminution of the number of polymorphonuclear leukocytes at the point of inflammation. The lymphocytes now begin to be more conspicuous in number. Their rôle, however, is less definitely determined. Some of them seem to undergo a swelling and transformation into the large mononuclear phagocytic cells that will be described below. It was formerly held that some of them become engaged in the process of reproduction of tissue, being first converted into formative or fibroblastic cells. This view is probably erroneous, the evidence being that neither the ordinary lymphocyte nor the variety known as plasma-cell has such a function.

The eosinophile leukocytes may sometimes be abundant in inflammatory exudates, and it has been suggested that they are active in throwing out bacteriolytic substances. Further proof of this assumption must be forthcoming.

In all of these processes in which the emigrating leukocytes are concerned soluble substances and enzymes are essential. These will be referred to after the liquid exudation has been discussed.

Large mononuclear phagocytic cells become conspicuous in the area of inflammation after the primary leukocytic phase begins to subside, and in certain inflammations they are so almost from the beginning. These cells are of variable size, always large, and sometimes of giant proportions. The rather large pale nucleus and the phagocytic property of the cells are their distinguishing characteristics. The general term "macrophages" may be used to designate them, though it indicates no special derivation. The origin, indeed, is still uncertain, but among the possible sources of derivation are the lymphocytes, the endothelium of lymph-glands and channels, blood-vessel endothelium, and various wandering tissue-cells. It is not probable that the fixed tissue-cells of the locality give origin to them. The macrophages are specially concerned in taking up leukocytes and fragments of cellular destruction. Sometimes a number of polymorphonuclear phagocytes, with their own inclusions, all more or less degenerated, are found within a macrophage, and there may be, in addition, red corpuscles and débris of other cells. The complete digestion of these contents may occur in part in the area of inflammation, but some of the macrophages, like some of the polymorphonuclear phagocytes, perhaps find their way to regional lymphatic nodes; and similar cells primarily make their appearance in the lymphatic nodes when the polymorphonuclear phagocytes invade these structures.

Giant-cells, containing multiple nuclei, are found in certain forms of protracted or chronic inflammation. They will be described later.

Exudation of Liquids.—Coincidentally with leukocytic emigration there is exudation of more or less altered blood-plasma. The amount of liquid exudation and the character of the exudation vary with the nature and condition of the tissue affected and the character of the irritant. In loose cellular tissues and in inflammation of membranes lining cavities large quantities of liquid are poured out of the vessels, while the reverse is seen in denser parts. Some intense irritants occasion free exudation, while others, by their very intensity or peculiar characters, at once destroy the tissues, and exudation is comparatively slight.

The exudate is richer in albumin and more coagulable than dropsical fluid, which is a further indication that the blood-vessels are more permeable in inflammation than in health or mere congestion. It is probable, moreover, that the capillary walls act in a secretory manner, as do the walls of the lymphatic channels. This would in some measure explain the difference between inflammatory exudate and dropsical liquids. The accumulation of exudate in the tissue may be so abundant that the term *inflammatory edema* is justified. In such cases, as in all inflammations to a less extent, the cause of the retention of liquid in the inflammatory area is in part a reduction of tissue tone or elasticity which prevents the movement of the fluid toward the efferent lymph-channels. Thrombosis of lymphatic vessels, induration of surrounding tissues, and edematous and cellular swelling of regional lymph-nodes are also causes for the retention of liquid exudate in an inflamed area.

After its exudation the fluid may undergo coagulation by interaction with fibrin ferment derived from disintegrated leukocytes, with formation of fibrin and consequent solidification of the inflamed area. When inflammations affect mucous membranes there is usually active stimulation of the epithelial cells and outpouring of mucus, which materially alters the exudate.

The exudate plays an important rôle in inflammation. Among its uses may be mentioned that it serves as a diluent of noxious bodies, that it brings from the blood substances that aid in destroying the irritants, and that it may carry similar substances derived from the leukocytes, either secretions or products of their degeneration. Occasionally it has the unfavorable action of carrying away and thus spreading throughout the system the causes (bacteria, for example) or products of the inflammation. In the case of fibrinous inflammation, the fibrin serves to strengthen the limiting wall by which an inflamed area is surrounded. The highly nutritious character of the liquid is doubtless of importance in the proliferative processes that are presently to be described.

3. Chemical Processes Involved in Inflammation.—Many of the features of inflammation have been made clearer by recent studies of certain chemical relations of the cellular and fluid exudates. It has been found that the leukocytes carry in their substance an active proteolytic enzyme which acts best in an alkaline medium. This enzyme doubtless

operates to dissolve bacteria and other albuminous bodies ingested by the phagocytic leukocyte. When this enzyme is liberated by disintegration of emigrated leukocytes it is capable of attacking the tissues and softening them or digesting them, but this result is prevented when sufficient fluid exudate is present, because the latter contains an anti-enzyme which destroys or in some manner neutralizes it. This is, perhaps, the same anti-enzyme which is present in normal blood-serum, and which is capable of restraining the action of trypsin. Should leukocytic exudation become excessively abundant, owing, for example, to virulent highly chemotactic micro-organisms, or should the physical nature of the tissues prevent an adequate fluid exudate, the amount of leukocytic enzyme liberated becomes disproportionate to the amount of anti-enzyme, and there results a proteolytic softening of the tissues and exudate with resulting pus formation. This disproportion of enzyme and anti-enzyme, therefore, determines the occurrence of suppurative instead of non-suppurative inflammation.

In the later stages of inflammation, when the leukocytes have largely disappeared and the mononuclear phagocytes are in evidence, a different proteolytic enzyme is found. This has been studied especially in tuberculous tissues with abundant epithelioid cells. This enzyme acts best in an acid medium, and is probably active in the destruction of leukocytes and various cellular remnants ingested by the macrophages, from which it is derived. Opie has suggested the names *leukoprotease* and *lymphoprotease* for the enzymes derived from the leukocytes and mononuclear cells respectively.

Other chemical processes besides those mentioned are involved in inflammation. The first effect of the action of inflammatory irritants, whether merely mechanical or micro-organismal, is cellular destruction, and consequent liberation of substances that are chemotactic and to some extent toxic. There follows the exudation of leukocytes and liquid. Chemical combination between fibrin ferment derived from disintegration of leukocytes or other cells and the liquid exudate causes fibrin formation, and thus some solidification of the inflammatory exudate. Later, this fibrin, together with the more or less degenerated cells in the area of inflammation, may be digested by the action of the leukoprotease before described, and perhaps by the action of similar if not identical enzymes derived from the blood-serum.

Micro-organisms call forth special chemical defenses. As has been related, the micro-organisms are in large part ingested by phagocytic leukocytes and are in some way destroyed within these. It has been shown that substances called opsonins are important in preparing micro-organisms for this ingestion by phagocytes, and probably bactericidal substances derived from the blood-serum in the inflammatory exudate, as well as precipitins and agglutinins, are also important agents in the preparation for phagocytic destruction of micro-organisms. It has, indeed, been shown that living and virulent organisms may be taken up by phagocytes, but their preliminary destruction or devitalization seems to be the rule. Some of the micro-organisms, doubtless, are destroyed

and carried off into the lymphatic channels without the aid of phagocytes. It is asserted by some observers that besides the enzymes of blood- and tissue-cells described above, there is in these cells a separate and extractable substance which can destroy bacteria. Its office in inflammation is not understood.

4. Proliferative Changes.—Sooner or later in an inflamed area, and especially at the periphery, there are evidences of cellular proliferation which occasions the appearance in the tissue of round cells closely resembling lymphocytes or mononuclear leukocytes. They differ, however, in being somewhat larger, in having a larger and paler nucleus, which is round or oval, and in their frequently exhibiting evidences of karyokinesis. These cells are direct derivatives of the fixed connective-tissue cells and of endothelium lining lymph-spaces. The parent cells first undergo enlargement by swelling of their protoplasm, then mitosis of the nuclei and cell division follow. The new-formed round connective-tissue cells may in part become wandering cells and more or less phagocytic, but the greater number remain fixed and become elongated or polymorphous in shape, produce intercellular substance, and thus assume a purely regenerative rôle. These are designated *fibroblastic cells*. (See Regeneration.)

At the stage under consideration the cellular elements of inflamed tissue consist of emigrated leukocytes, now reduced to a small number, many lymphocytes, large mononuclear leukocytes, and round connective-tissue cells. The appearance is characteristic of the more advanced stages of acute inflammation and of chronic inflammation. It is termed *round-cell infiltration* (Fig. 28).

Virchow held proliferative changes to be the essential feature in inflammation, and believed that all round cells are concerned in this process; Cohnheim denied that proliferation is the important feature of inflammation, and ascribed to emigration the essential rôle. Later, it was held that the proliferative changes are not, in reality, a part of

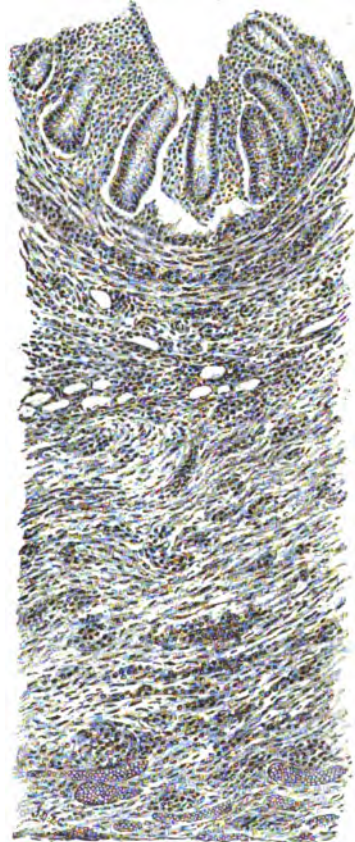


Fig. 28.—Acute appendicitis, with extensive round-cell infiltration of all of the coats of the appendix.

inflammation, but rather regenerative and for the purpose of repairing the tissue injuries after inflammation (Fig. 29). At the present time many regard as factors in inflammation both emigration and proliferation, whether the latter in any individual case is due to direct stimulation of the cells, or is secondary to destructive changes, or is merely the result of increase of nutrition from the inflammatory congestion. It is conjectured by some that under chemotactic influences the cell contents of fixed cells are incited to movements terminating in karyokinesis, just as the whole cell is influenced in the case of movable cells. The proliferation of the fixed connective-tissue cells may be an early process, but does not usually occur until some time after the exudative changes have taken place. The new-formed cells have at first the characters above described, but later they become irregular and many of them spindle shaped (formative cells or fibroblasts). In chronic

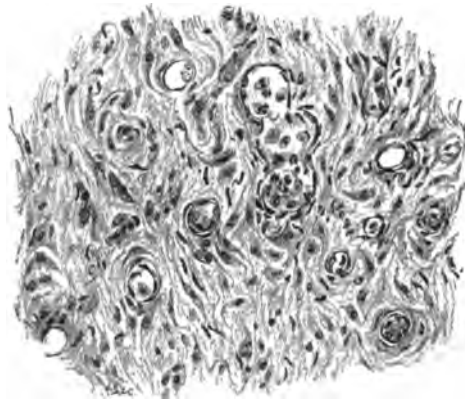


Fig. 29.—New blood-vessels and fibroblastic cells in a beginning adhesion of the pericardial layers.

inflammations, especially such as surround foreign bodies, giant-cells are found. These have distinct phagocytic functions.

Giant-cells may be divided into: (a) *Foreign body giant-cells* with peripherally located nuclei and a homogeneous, somewhat degenerated center. They arise in degenerating tissue, probably by coalescence of multiplying endothelial or large plasma-cells. Some authors think they are due to direct nuclear division or nuclear division too rapid for the protoplasm to keep pace with it. (b) *Myeloplaxes* are giant-cells with uniformly distributed nuclei and a homogeneous protoplasm such as are seen in the bone-marrow and tumors. (c) *Parenchymatous giant-cells* are found in tumors, in regenerating interstitial tissues, or in the parenchyma of organs. The nuclei may be irregularly distributed, but are commonly connected by narrow isthmuses of chromatin. They arise by rapid nuclear division.

Granulation Tissue.—When the proliferative changes are active, new blood-vessels, formed by multiplication and lateral outgrowth of

the endothelium of the pre-existing vessels, are a conspicuous feature. These, surrounded by the various forms of round cells above described, and sometimes giant-cells, constitute granulation tissue. (See also Repair of Wounds and Regeneration.) Such granulation tissue is especially conspicuous on the floor of ulcers, and exemplifies the regenerative processes which follow immediately in the wake of the frank inflammatory reaction.

Proliferative Changes in the Parenchymatous Cells.—Swelling and, later, mitosis may occur in the early stages of inflammation, but are of slight extent. In certain chronic inflammations also, such as some forms of cirrhosis of the liver, proliferation of parenchymatous cells may be observed. In the latter instance the process is rather definitely of regenerative character. The changes in the earlier stages of inflammation are more truly inflammatory, though the new-formed cells, unlike some of the proliferative connective-tissue cells, do not migrate or take on phagocytic action.

5. Degenerative Changes in the Tissues.—The first attack of inflammatory irritants is made upon cells of fixed tissues, that is, upon cells of the parenchyma of an organ, upon the connective-tissue cells, or upon the walls of blood-vessels. The emigration of leukocytes and their combat with the irritants follows. In the case of bacteria which contain within their substance positively chemotactic bodies, it would seem probable that there is an immediate activity of these bodies; but various considerations make it more probable that even in the case of bacteria the first effect is exercised upon fixed cells. In the case of mechanical irritants damage or complete destruction of cells is the first step toward inflammation. Weigert, Neumann, and others hold that the "primary effect" in inflammation is always such tissue injury, which, in turn, excites exudation and, later, proliferation. The demonstration that tissue degenerations liberate positively chemotactic substances explains how the phenomena of inflammation are brought about. The degenerative changes may be merely physiological (some form of altered functional activity), or there may be structural alterations, such as cloudy swelling, mucoid degeneration, liquefaction, fatty change, coagulation, or other forms of necrosis. The nature of the degeneration depends largely upon the severity of the irritation. Very powerful irritants cause necrosis at once, and not inflammation. It is the irritants which disorder, but do not entirely destroy, cells that are especially apt to excite inflammation. The cellular degenerations now under discussion are entirely different in significance from the more conspicuous *secondary cellular degenerations* considered below. The primary degenerations occasioned by the first attack of the irritant are often inconspicuous and inferential rather than demonstrable.

Secondary Cellular Degenerations.—When inflammations attack tissues containing epithelia or other parenchymatous cells the latter often suffer secondary degenerative changes, cloudy swelling, fatty or mucoid degeneration, and total necrosis. These secondary cellular changes may serve to spread and intensify the original inflammation,

and are, moreover, especially harmful to the functional activity of the diseased organ or tissue. The cause of these degenerations may be the same toxic agent which initiated the whole process or, on the other hand, the pressure of exudates and the circulatory disturbances incident to the inflammation.

Etiology.—Irritation by mechanical, chemical, thermal, or infectious agents causes inflammation when it is severe enough to disturb the vitality of the tissue and not sufficient to cause extensive necrosis at once. When the irritant is brought to bear upon the tissues directly, there is probably, first, cell degeneration, followed by vascular disturbances and emigration. Micro-organisms may act by first destroying the cells, or may liberate from their substance some poison (protein) which is irritant and chemotactic. Disturbances of circulation, innervation, or metabolism may so alter cellular processes as to occasion the liberation of irritating and chemotactic products.

In the experience of surgeons bacteria stand out conspicuously as the almost invariable cause of "inflammation." This term, however, is used in a clinical rather than a true pathological sense. The processes concerned in the healing of uninfected wounds and in other cases of injury unaccompanied by infection are just as truly inflammatory. It must be recognized that non-bacterial injuries to tissues liberate substances by cell destruction which are capable of producing the phenomena of inflammation. Among the causes of inflammation in this pathological sense must be included certain endogenous processes, notably of circulation, innervation, and metabolism, which cause local cellular degeneration, followed by exudative and reparative phenomena.

Special Forms of Inflammation.—Various classifications may be used in describing forms or types of inflammation. The most natural is that which follows the anatomical changes. Thus we may distinguish (1) *exudative* inflammation, or the form in which the fluid and cellular exudation from the blood-vessels is the predominating element in the pathological process; (2) *parenchymatous* or *degenerative* inflammation, or the form in which destruction of the parenchyma cells is the leading feature; and (3) *productive* inflammation, in which proliferation is the striking characteristic. The nature of the cause, as well as the resistance of the organism or of the affected part, determine the particular form in a given case.

A number of subvarieties may be described, but it must always be remembered that inflammation is essentially the same in all cases. The three processes—exudation, degeneration, and proliferation—are present in greater or less degree in all forms, although in some cases one feature, in other cases another, may be most conspicuous.

Types of Inflammation.—1. **Edematous or serous inflammation** is characterized by a copious exudation of fluid with comparatively little cellular matter, as in edema of the larynx, serous effusions in the serous sacs, etc. The local forms of edematous or serous inflammation are usually expressions of intensely irritant causes; the serous

inflammations of serous cavities, however, are not necessarily of this severe grade. Indeed, in many cases serous inflammation may be a mild, subacute or chronic, process, which may subside gradually, leaving the serous membranes slightly thickened or adherent. This adhesion is due to the fact that fibrin collects upon the serous surface during the acute stage, the fluid remaining free in the sac. The fluid is removed by absorption; the fibrin, by digestion. Lasting adhesions remain when proliferative changes are firmly established before the digestive processes can complete their work of removing the fibrin deposits. The fluid in inflammatory exudations differs from dropsical fluid in containing more albumin, leukocytes, and fibrin factors.

2. Fibrinous Inflammation.—The plasmatic and cellular exudate may form a fibrinous membrane on free surfaces or a network within the tissues; this is termed “fibrinous inflammation” because the most conspicuous physical change is the excess of coagulum.

In purely fibrinous inflammations of serous surfaces there is a whitish or yellowish-white deposit of variable thickness, which is more or less adherent to the underlying surface. When removed, there may be seen beneath it a pronounced injection of the blood-vessels and roughness and rawness of the surface. This is due to beginning granulations. (See Repair of Wounds.) Microscopically, the fibrinous deposit consists of an irregularly arranged mass of fibrillar, granular, or homogeneous fibrin, with leukocytes and endothelial cells (more or less degenerated) enclosed in the deposit. The fibrin may be found in star-like formations made up of a more or less degenerated central leukocytic mass and radiating threads of fibrin extending from it in every direction. This may be significant of the liberation of fibrin ferment from the degenerating cells and consequent formation of fibrin about this as a center. Some authorities believe that fibrinous inflammation can never occur independently of destruction of fixed cells. In other words, they doubt the possibility of fibrin formation from purely exudative elements. Some experimenters have, however, described fibrinous inflammations of serous surfaces with an unbroken lining of endothelial cells under the fibrinous deposit, and have concluded that the fibrin is wholly exudative. Others regard the lining cells as cells of lymph-spaces, and not the original surface cells; and consequently conclude that cellular destruction always plays a part in the fibrin formation. Fibrinous inflammation in serous sacs is often associated with serous exudation, and the term *serofibrinous* is applied. In other cases (especially in peritoneal inflammations) the exudate is likely to become purulent—*fibrinopurulent* inflammation.

Inflammations of the serous membranes are nearly always more or less fibrinous.

3. Pseudomembranous or diphtheritic inflammation differs from the last in having associated with the coagulation of the exudate decided coagulation necrosis of the cells of the part inflamed. The difference is one of degree rather than of kind, and is largely dependent upon the character of the tissue in which the inflammation occurs. Diph-

theritic inflammation occurs especially in the pharynx and larynx, where it occasions pseudomembranes (Fig. 30). This is most frequently due to the specific bacillus of the disease called diphtheria; but diphtheritic inflammation may result from a variety of severe irritants, such as other bacteria, superheated steam, and chemical agents. The diphtheritic membrane consists of a network of fibrin or of homogeneous or granular fibrin masses enclosing degenerated epithelial cells and emigrated leukocytes. Sometimes it is quite superficial, involving only the surface layer of epithelium; at other times the whole depth of the mucous mem-

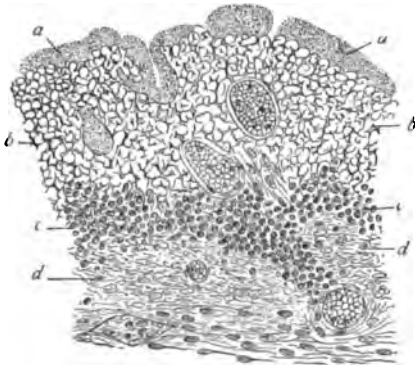


Fig. 30.—Pseudomembranous inflammation of the uvula: *a, a*, masses of micrococci; *b, b*, necrotic cells; *c, c*, round-cell infiltration; *d, d*, fibrin network (Ziegler).

brane is implicated. The former are sometimes called croupous and the latter diphtheritic false membranes. These terms, however, are ill-defined and objectionable. The use of the terms *fibrinous* and *pseudomembranous*, omitting *croupous* and *diphtheritic* as unnecessary, if for no other reason, is good practice. In any event it must be observed that the term "diphtheritic" as used in this place refers to a type of fibrinous inflammation rather than to a process due only to the diphtheria bacillus. This organism is the most

frequent cause of such inflammation, but other agents, as before noted, occasion the same type of inflammatory lesion.

4. **Suppurative inflammation** is characterized by unusual abundance of emigrated leukocytes and by the tendency to liquefaction. Bacteria are most frequently the cause; but it has been shown experimentally that croton oil, calomel, turpentine, and other substances are capable of producing suppuration. Of the bacteria, the commonest are the so-called pyogenic staphylococci and streptococci; but numerous forms, not commonly pyogenic, may occasionally prove so. Such are the bacillus of typhoid fever, the gonococcus, the *Bacillus coli*, and others.

The implantation of bacteria of suppuration at the point of disease may take place directly through wounds, or somewhat indirectly through the circulation, the micro-organisms having gained access to the system through small abrasions in the mucous membranes or skin. Some local injury may then serve to determine the suppurative inflammation at a given place.

Recent studies ascribe to chemotaxis the important rôle in the action of bacteria in inflammation and suppuration. Either the products of the bacteria or substances derived from their own protoplasm (endogenous substances) exercise a powerful chemotactic influence, and thus occasion the massing of emigrated leukocytes (Fig. 31). The preponderance of cellular over liquid exudation and the consequent excess

of leukoprotease over anti-enzyme prevent fibrin formation, or cause a solution of fibrin already formed and a liquefaction of degenerated tissue elements and cells. The sequence of events is as follows: bacteria directly implanted in the tissue or carried to the capillaries in the bloodstream first cause local cellular changes (degeneration or necrosis); then congestion and exudation of leukocytes and plasma occur around this focus; next more or less fibrin formation results from the exudation, and finally, after more and more leukocytic emigration, softening of the whole area completes the formation of pus. The essence of suppurative inflammation is the excessive emigration of leukocytes, the softening of the tissues, and the failure of the fluid exudate to coagulate and form fibrin. The excessive leukocytic invasion is chargeable to inordinate chemotaxis due to the micro-organismal or other causes of the inflammation or to their products.

Pus consists of a liquid part, the *liquor puris*, a modified blood-plasma, which differs from ordinary plasma in being less coagulable and in containing notable quantities of albumose (peptone); and a corpuscular part, consisting chiefly of polymorphonuclear leukocytes more or less degenerated. The leukocytes are chiefly polymorphonuclear and filled with neutrophilic granules. Nevertheless it is not possible to identify these pus-cells absolutely. They often contain globules of glycogen and fat. Some proliferated connective-tissue cells or wandering cells may be added from the neighboring tissue, but these constitute but a minority of the whole number. The pus-cells present a distinctly granular protoplasm and fragmented nuclei.

Abscess.—When circumscribed supuration occurs in the substance of a tissue or organ, the lesion is called an abscess. This consists of a collection of pus which usually has a creamy yellow color, but may be variously altered by subsequent changes. The abscess grows by further liquefactive changes in the surrounding tissues because of the attraction of leukocytes with their ferments from the hyperemic vessels in the peripheral structures. Around the abscess the tissues present an indurated zone or wall in which the proliferative changes and fibrin formation described as part of inflammation are conspicuous features. There are numerous round cells, differing from emigrated leukocytes and often showing mitotic figures in the nuclei, and there are new blood-vessels and beginning organization. (See Regeneration.) Fibrin in the form of interlacing threads or in masses, the product of plasmatic exudate and of coagulation necrosis, adds to the embankment. In

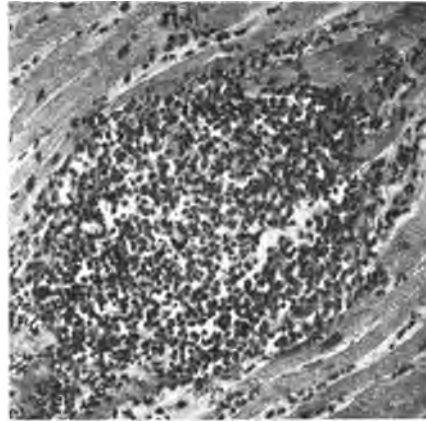


Fig. 31.—Embolic abscess in the myocardium, showing accumulation of large numbers of leukocytes (Karg and Schmorl).

slowly forming abscesses the surrounding wall of condensed tissue is often quite firm. This restraining wall was formerly erroneously regarded as a pus-producing membrane, and, therefore, called the *pyogenic membrane*. As a matter of fact, on the contrary, it represents the inflammatory changes at the periphery of a suppurating area where the actively chemotactic effects of the pyogenic agent are sufficiently reduced in activity that the liquefaction characteristic of pus formation is minimized in favor of coagulation and formative processes.

Abscesses tend to soften the surrounding tissues in the direction of least resistance, and thus to break on the surface, discharging their contents by sinuous tracts or *sinuses*. This discharge not only evacuates the pus, but reduces pressure and permits a renewed flow of fresh blood through the so-called pyogenic membrane, bringing with it the anti-enzymes and bacterial antibodies of the serum. Sometimes the pus of an abscess becomes inspissated by absorption of the liquid part, and the residue undergoes various degenerative changes, such as mucous, fatty, or calcareous. At the same time the surrounding membrane may advance to complete organization, and thus encapsulates the abscess.

Phlegmonous Inflammation.—Suppurative inflammation may have a less definitely circumscribed character than that seen in abscesses. It may take the form of a *purulent infiltration* in which the tissues are extensively infiltrated with emigrated leukocytes and more or less softened by liquefactive processes, or by abundance of fluid exudate that does not coagulate. In other cases a nearer approach to the conditions seen in abscesses is observed when the purulent process spreads along planes of tissue or neighboring foci coalesce to form a diffuse suppurative condition. To this the terms *phlegmon* and *phlegmonous inflammation* are applied.

Ulcer.—Suppurative inflammation with erosion of areas of the skin or mucous surfaces occasions ulcers. The floor of an ulcer has the same histological construction as the wall of an abscess. In it may be seen small red points or granulations, which consist of loops of capillary blood-vessels surrounded by round cells. (The histology of granulation tissue is more minutely described under Regeneration.)

The clinical features of ulcers vary widely. Sometimes rapid destruction of the tissues causes large and spreading ulcers, called *phagedenic*. Others extend in one direction while healing in other parts, and are called *serpiginous*. The granulations may be too rapid in growth, forming red fungous masses (proud flesh) which fill up the ulcer. In other cases the ulcer remains dry and *indolent*, showing little tendency to heal.

Some ulcers are not primarily of inflammatory origin. For example, the *round* or *peptic ulcer* of the stomach is formed by digestion, through the action of the gastric juice, of a part of the stomach which has become lowered in vitality or possibly necrotic. Similarly, the beginning change in the *perforating ulcer* of the foot in tabes and in decubitus (bed-sores and other forms of pressure ulceration) is not inflammatory, but,

rather, necrotic. Secondly, however, the necrotic tissues in these cases become active irritants and occasion true inflammatory ulceration.

Suppurative inflammations of serous membranes lining closed sacs cause collections of pus in the cavities. The pus usually contains more or less fibrin, and there is a fibrinopurulent exudate on the serous surface.

Suppurative inflammation of the skin and subcutaneous tissues may be localized or diffuse. Of the localized type, there are various *pustules*, *furuncles* or *boils*, and *carbuncles*.

A furuncle is a suppurative and necrotic inflammation beginning in one of the sweat-glands, sebaceous glands, or hair-follicles. A carbuncle is a more extensive but similar process beginning in several of the glands or hair-follicles simultaneously, and causing considerable necrosis or gangrene of the skin and subcutaneous tissue.

5. Hemorrhagic Inflammation.—More or less diapedesis of red corpuscles generally occurs in inflammation; but sometimes the irritating cause falls with such peculiar force on the blood-vessels or the general condition of the patient (cancer, tuberculosis, hemophilia, scurvy) is such that the exudate is unusually rich in red corpuscles. Certain micro-organisms (organisms of hemorrhagic septicemia) more or less regularly cause hemorrhagic inflammation. Intravascular thrombosis and obstruction of capillaries with masses of micro-organisms play an important part in causing the hemorrhagic exudation. These are always serious inflammations, and are to be distinguished from ordinary inflammations in which accidental hemorrhage occurs. Hemorrhagic inflammation, in a pathological sense, may be an early stage of other forms, particularly of the fibrinous variety of the lungs. There is severe congestion, diapedesis, and transudation of plasma, which almost at once make fibrin. This hemorrhagic state is transient and is not to be compared with the continued outpouring of blood in the hemorrhagic infections. The cause of the last is bacterial toxins acting upon vessel walls, decreasing their resistance. The effect is greatest where they are naturally thin, in a condition of stasis or already affected by local or general disease (syphilis).

6. Catarrhal Inflammation.—This term is used to designate inflammations of mucous membranes. The character of the inflammation depends to a large extent upon the individuality of the mucous membrane affected, differing greatly in the nose, throat, stomach, bowel, etc. There is always considerable congestion of the mucosa, and generally a great deal of serous exudation, which is discharged from the surface as a rule, but is to some extent retained in the tissue, causing edematous swelling. This is especially marked when the submucosa is considerably implicated. The epithelial cells of the surface suffer degeneration (mucous or fatty) and necrosis, and are discharged with the serous exudate; they may be recognized as goblet-cells (mucous), or as granular cells (fatty), or as fragmented necrotic structures. Coincidentally with the serous exudation, and in greater measure after the latter has become less marked, leukocytes escape from the blood-vessels or emi-

grate from their resting-places in the submucosa and make their way to the surface between the epithelial cells (Fig. 32). At this stage also mucus becomes a more or less pronounced feature in the exudate. There is little fibrin formation in catarrhal inflammation, since the exudate moves toward the surface and escapes. The features of this form are the superficial exudation and desquamation after degeneration. When fibrin appears this catarrhal form becomes pseudomembranous.

When in great abundance (as in some nasal catarrhs) the process may be a *purulent* or *suppurative* one; more frequently there is sufficient mucus to require the term *mucopurulent*. Superficial erosions of the epithelium and hemorrhages are frequently met with.

When catarrhal inflammations are chronic, there is usually considerable *productive inflammation*, with consequent thickening, and later, when the new fibrous tissue contracts, there may be uniform thinning

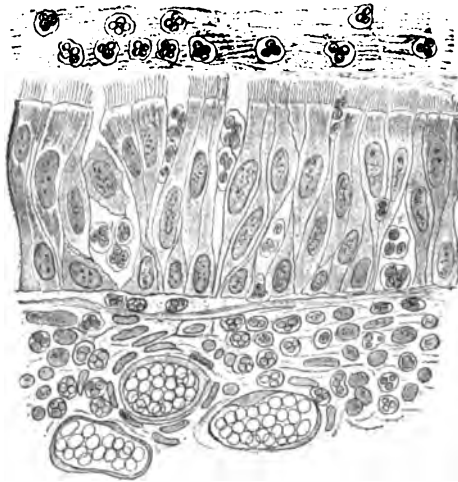


Fig. 32.—Acute bronchial catarrh, showing the escape of leukocytes from the submucous tissue between the epithelial lining cells (Thoma).

of the mucosa or irregularly distributed areas of hyperplasia intermixed with areas of thinning. In some cases, however, progressive atrophy of the mucosa occurs without previous productive changes. This is especially marked in the bowel, where, doubtless, constant distention plays an important part. When the contractions of the fibrous tissue are irregular, the mucosa between the fibrous areas may be elevated, especially if there is at the same time proliferation of the surface epithelium and the glandular elements in the mucosa. In such cases a granular surface or polypoid elevations result. These are common in the stomach and the bowels.

7. Parenchymatous or Degenerative Inflammation.—This term may be applied to certain inflammations, such as forms of nephritis in which degeneration (cloudy, fatty, etc.) of the parenchyma cells is more conspicuous than the exudative processes. The changes in the parenchyma

in such cases are often secondary to the inflammation; in other cases they are precedent. Strictly speaking, the parenchymatous changes are not essentially a part of the inflammation, but in those cases in which much degeneration of parenchymatous cells accompanies inflammations the term "parenchymatous inflammation" is convenient and expressive.

8. **Necrotic or gangrenous inflammations** depend for their occurrence upon the severity of the irritation or the state of the general system.

9. **Productive Inflammation.**—In this form the proliferative changes predominate over exudation and degeneration. This may be due to the nature of the etiological factor, to peculiarities in the tissue reaction, or local conditions affecting the removal of the irritant. In all cases in which inflammation for any of the above reasons becomes chronic the proliferative changes in the affected tissues become more or less predominating. Some degree of primary tissue destruction appears to be essential to the productive process, which, therefore, must be regarded as always reactive or regenerative.

It is desirable to differentiate between (a) productive processes as the last stage of acute inflammation, (b) the newly formed connective tissue as the result of acute inflammation, and (c) the progressive production of fibrous tissue as the result of continued irritation. The lines between the three are not sharp. The repair of serous membrane inflammation may be a simple thickening of the layer itself, but if granulations attach two or more areas together, we have adhesions which are in excess and probably not necessary for the healing of the original defect. Thus, again, in cicatrices we have nature's expression of excessive production for repair. When the cause of the inflammation ceases the productive changes usually cease, unless the tissue already made acts as a foreign body and continues as a mechanical irritant. If it cease, we have a finished reparative process as the result of inflammation. Should the irritant continue its action, there is continued response as expressed in the infectious granulomata and chronic fibroses. The last are really *chronic inflammations*.

Repair of Wounds.—Productive inflammation is well illustrated in the healing of wounds. If the lips of a clean, incised wound are drawn together at once and kept closely apposed, rapid healing occurs, which is called *healing by immediate union*. In these cases a microscopical examination shows slight exudation from the surfaces of the wound and proliferated connective-tissue cells. The epithelial continuity is restored by proliferation of the old epithelial cells. Should apposition be less immediate or less accurate, the amount of exudation is greater. If the wounded surfaces are examined twenty-four hours after the injury, they are found red and swollen and soon they become glazed in appearance. The microscopical features here are the same as in the case of healing by immediate union, excepting the amount of exudation is greater. Healing proceeds in the same way, but more slowly, and is called *healing by first intention*. In neither case is there great congestion. If the wound be irritated by foreign bodies or kept exposed, there will be seen on the sur-

faces, after two or three days, small red elevations, known as *granulations*, which consist of loops of new-formed capillaries covered by emigrated and new-formed round cells, and sometimes (after longer intervals of time) giant-cells (Fig. 33). The surface may be covered with considerable pus. The proliferated round cells gradually elongate and form new fibrous tissue (see Regeneration), which afterward contracts, forming *cicatrices* or *scars*. The epithelial continuity is re-established by multiplication of the old epithelial cells at the edges of the wound. This form of healing is called *healing by second intention* or *healing by granulations*.

The **formation of adhesions** following inflammation of the serous surfaces occurs in much the same way as wounds heal. The primary exudation is largely fibrinous and causes agglutination of neighboring surfaces. Subsequently the proliferative connective-tissue cells, having become actively wandering cells, penetrate this fibrinous exu-

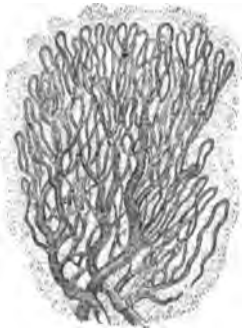


Fig. 33.—Loops of blood-vessels in granulation tissue (Thiersch).

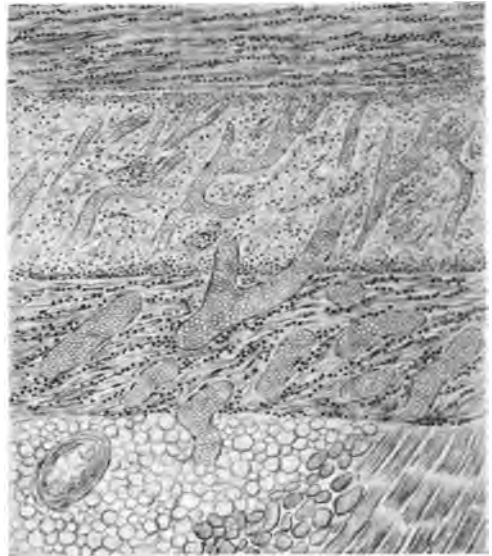


Fig. 34.—Adhesive pericarditis, showing fibrin deposit, with new blood-vessels extending upward into it.

date, as do new-formed blood-vessels (Fig. 34). Thus a union of vascular channels is effected between the adjacent inflamed surfaces, and organization follows.

Precisely similar changes occur in the tissues surrounding a foreign body, as a piece of sponge or around a portion of dead tissue. In these cases the exudative and proliferated cells tend to penetrate into the foreign mass, as occurs also in the organization of thrombi. There is in these cases a greater tendency to the formation of giant-cells than in ordinary granulations. If the foreign mass can be softened and absorbed, this gradually occurs, and later merely a scar will remain; if it cannot be absorbed, connective tissue eventually encloses or encapsulates it.

General Fibrosis.—A tendency to widespread productive inflammation is noted in certain individuals. This affects the blood-vessels especially (general arteriocapillary fibrosis, general angiosclerosis), and

also the liver (cirrhosis of the liver), the kidneys (interstitial nephritis), and other organs (Fig. 35). Some form of degeneration or necrosis of the parenchymatous cells is doubtless the preliminary stage in all of these cases. First the endothelia or the muscle cells are affected in the cases of blood-vessels; the hepatic cells in case of the liver; the epithelia of the tubules and glomeruli in case of the kidney, etc. The resulting fibrosis is, however, out of all proportion to any demonstrable change of parenchyma. In some cases it is evident that the fibrosis is merely a compensatory regeneration to replace degenerated parenchyma and that the process is not primarily inflammatory, although some of the histological changes are akin to inflammation. It is asserted that the cause of this degeneration of parenchyma cells may sometimes be repeated protein intoxication. (See Anaphylaxis.)

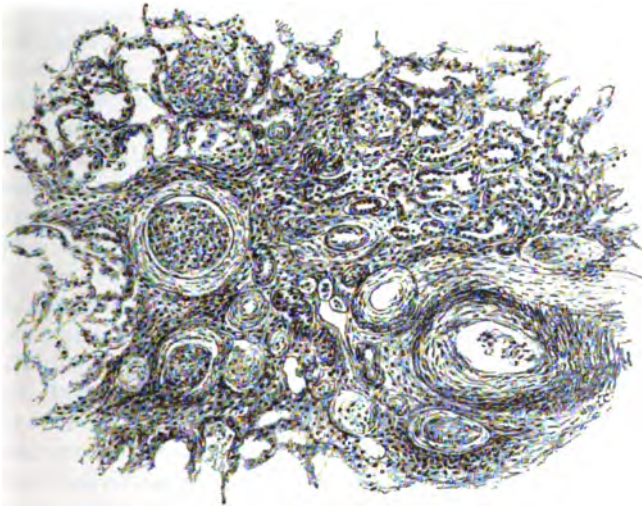


Fig. 35.—Chronic interstitial nephritis: great increase of connective tissue around the glomeruli, renal tubules, and blood-vessels; from a case of arteriocapillary fibrosis.

Productive inflammation may effect other tissues than the fibrous connective tissues. Reference has already been made to epithelial proliferation in the healing of wounds. Similar epithelial processes of greater activity or duration may lead to warty growths of the skin or polypoid outgrowths on the mucous membranes. In pharyngeal catarrhs considerable proliferation of the adenoid tissues is not unusual. So also thickening of cartilages, bones, or the periosteum is not an unusual result of inflammation of these structures.

Pathological Physiology.—Inflammation represents increased and altered activity of tissues as a result of irritation; its primary object is the removal of the irritant. It is a pathological state *per se*, but considered from the point of view of its result (the removal or confinement of the irritant and the resulting tissue destruction) inflammation is essentially conservative and useful. In this process no new forces or activities are

involved: the phenomena are all observed in normal tissues, though to a less degree and in more orderly behavior. The liquid and cellular exudation has its prototype in the formation of lymph and in the normal wandering cells of the tissues; the increased vascularity is the result of increased demand, and is abnormal in degree only; the cellular destruction is an accentuation of the ordinary death of cells resulting from wear and tear, though the form of the cell destruction is more violent and probably different; the postinflammatory regeneration is effected by karyokinetic multiplication of cells, as in normal tissues.

In the destruction and removal of the irritant, phagocytosis (*q. v.*) is important; it is accomplished by the leukocytes, by endothelial cells, the wandering connective-tissue cells, and giant-cells.

Though a local process, inflammation often has widespread results. The causes of the inflammation gain access to the blood via the lymph-vessels and regional nodes before a wall of fibrin and leukocytes has been built up around the inflamed locality. When once the local tissue reaction has developed and the lymph-nodes are prepared, further dissemination is halted. The primary invasion of the blood-stream may be advantageous in stimulating the antibodies of the body, which can then be carried to the focus of infection in the blood-plasma. The products of tissue change (primary cellular necrosis, degeneration of the emigrated leukocytes, softening of the tissue and coagulated exudate) entering the blood may occasion fever and other evidences of toxemia.

The functional activity of a part the seat of inflammation is often increased, though somewhat altered. An inflamed gland may produce an excessive but abnormal secretion. In other cases functional activity is lessened; chronic inflammations almost certainly lessen functional power. Secondary parenchymatous changes, by altering organic action, may be highly injurious to the whole organism.

Resolution after Inflammation.—In cases of trivial exudation the emigrated leukocytes may re-enter the blood-current through the lymphatics. The liquid exudate is similarly disposed of, while the proliferated connective-tissue cells remain *in loco* or become wandering cells. When the exudate is more abundant, the liquid elements may be removed in the same way, but the cells first undergo degenerative softening and are reduced to the form of an emulsion, which is gradually absorbed. In purulent inflammations the pus may be discharged through external openings or into cavities of the body or may become inspissated. (See Purulent Inflammation.) The degenerated parenchyma in inflammation may recover if the degeneration is not severe, or may be softened and removed. Phagocytic cells play a prominent part in the removal of broken-down cellular remains, pigment masses, and the like.

The reparative changes in inflammation may be so slight as to lead to no discoverable lesion after the process is completed; but when large damage has been done there is apt to be a permanent scar or some other productive lesion.

Specific Inflammations or Infectious Granulomata.—Tuberculosis.

Structure and Evolution of the Tubercle.—When the tubercle bacillus is received into any tissue or organ, its first effect, according to the investigations of Baumgarten, is to stimulate or irritate the fixed connective-tissue elements and endothelial cells and cause a proliferation of round cells, which resemble in their abundance of protoplasm the epithelial cells, and are, therefore, known as *epithelioid* cells. These have usually a single nucleus, of rather clear vesicular appearance, not deeply staining, and a relatively large amount of protoplasm. They may be produced in greater or less abundance, as the first reactive change of the tissues to the irritation of the tubercle bacilli. They represent primarily the cellular reaction on the part of the endothelial and fixed tissue cells, and later assume a fibroblastic character. Next there follows an infiltration with leukocytes from the surrounding blood-vessels or lymphoid collections common to all tissues, and the focus of irritation thus becomes surrounded with numerous small round cells, mostly mononuclear, with darkly staining nucleus and a small protoplasmic body (Fig. 36). In more acutely formed lesions polymorphonuclear leukocytes are more abundant. This leukocytic infiltration represents the reaction of the vascular system to the tuberculous irritation or infection. The number of small round cells varies greatly in different instances. Sometimes, as in certain tubercles of lymphatic glands, they may be relatively few, while the epithelioid cells are present in abundance. In other cases the leukocytes are so quickly attracted and in such numbers that the tubercle seems composed of these cells alone, no epithelioid cells appearing in view. These tubercles are known as the "lymphoid." In the later stages the round cells may disappear by degeneration, exposing the previously hidden epithelioid cells.



Fig. 36.—Miliary tubercles in the liver, showing abundant round cells in the peripheral parts, epithelioid and giant-cells within.

At the stage of the tubercle when it is composed mainly of epithelioid and lymphoid cells it appears to the naked eye as a grayish, somewhat translucent, pearly body. It is *avascular*, no tendency toward formation of new blood-vessels being apparent. In the further evolution of the lesion degenerative changes take place. These are hyaline degeneration, coagulation necrosis, fatty change, and eventually a transformation into cheesy material, the so-called caseous necrosis. These changes result from the specific action of the tubercle bacillus, though in part also from the avascular condition of the tissue. Avascularity alone, however, is not the cause of caseous necrosis. One of the

first changes noted is a granular change in the cell protoplasm which lessens the affinity of the cell protoplasm and of the nucleus for ordinary stains. There may be seen among the cells of the tubercle here and there individuals which show this beginning necrosis. These are usually grouped in the center of the tubercle, though at times also at different points. The outlines of these cells become less distinct and they are progressively less deeply stained, until with advanced necrosis the cell is broken down into particles or débris (Fig. 37). In the early stages of necrosis the epithelioid cells tend to form giant-cells either by coalescence of neighboring epithelioid cells or by division of the nucleus without division of the cell body. This is the Langhans giant-cell with its nuclei arranged about the periphery. The giant-cell is not characteristic of tuberculosis, as it may be found in many of the specific inflammations and also in foci of chronic irritation due to foreign bodies,

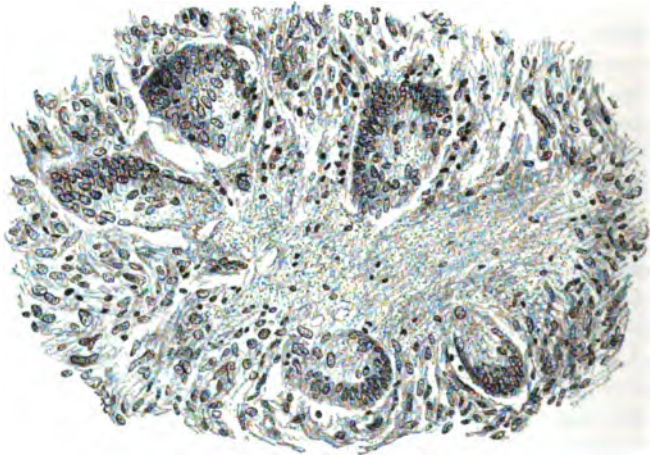


Fig. 37.—Large tubercle of the lung, showing cheesy necrosis in the center; the epithelioid and giant-cells around the cheesy center are more or less degenerated.

as well as in tumors. In no condition, however, are they so abundant or so conspicuous as in tuberculosis. In some cases they may not be seen in the tubercles at any stage. In other cases they are very numerous. The giant-cell falls an early victim to the advancing necrosis. Perhaps, in fact, the formation of the giant-cell is an evidence of beginning necrosis and the division of nuclei without division of the cell is an evidence of the degenerative change. As necrosis of the cell advances the protoplasm becomes granular and opaque, and eventually breaks down completely. This change usually occurs at the opposite side of the cell from that in which the nuclei are gathered; or in cases in which the nuclei are near the periphery of the cell the necrotic changes begin in the center. Finally, a tubercle undergoes almost complete necrosis and is transformed into a cheesy mass, the surrounding connective tissue perhaps still showing proliferative changes which may eventually cause encaps-

sulation of the tubercle. Calcification may ensue in the cheesy mass and thus lead to permanent arrest of activity in the nodule.

The *foreign body* tubercle, that due to pieces of silk, hairs, etc., usually under the skin, differs from the specific kind in failing to undergo caseation, and in the prominence of connective-tissue new growth with some giant-cells. Tubercles arising from acid-fast organisms not the true tubercle bacillus are almost exactly like the specific tubercle and must be differentiated by bacteriological methods (Fig. 38).

In the growth of tuberculosis the normal tissue elements of the part effected are pushed aside, or may be softened and destroyed by the disease processes. The connective-tissue fibers of the part, however, are longest retained, and remain as a reticulum or tubercle stroma long after the other elements of the tissue have disappeared or been pushed aside.

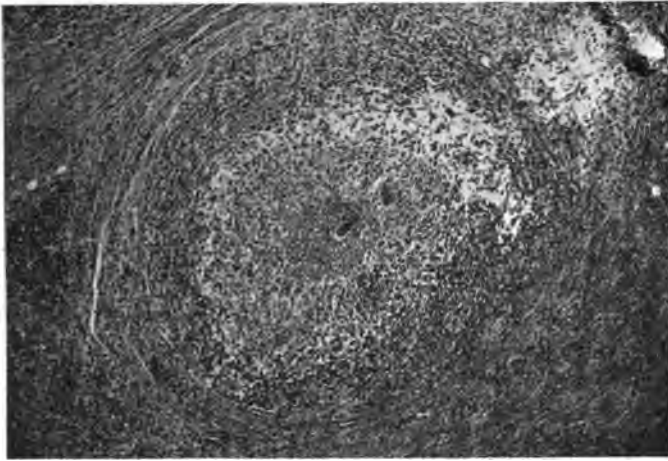


Fig. 38.—Foreign body tubercle in subcutaneous tissue, showing foreign body (wood) in the center and an atypical giant-cell.

In soft tissues, such as the lungs, spread of tuberculous lesions is easy, and a diffuse inflammatory exudate may arise with only an occasional miliary tubercle. If several tubercles meet, their limiting walls may fuse and a conglomerate tubercle ensue. A conglomerate tubercle may also arise by the transportation of organisms from the center of an already formed focus, through its outer zone, by means of epithelioid cells or lymph-currents.

Tubercles tend to coalesce, forming larger tubercular masses, and sometimes distinct tuberculous tumors are so produced. In the lower animals, particularly in cattle, such tuberculous tumors of the serous surfaces are not uncommon. They may simply stud the membranes, or they may hang as polypoid masses; the term "pearl disease" is applied to these cases (Fig. 39). Somewhat similar tuberculous tumors are met with in human tuberculosis, especially in the brain (Fig. 40). As a rule, however, increasing areas of tuberculous disease of organs are only



Fig. 39.—Miliary tubercle of the human form.



Fig. 40.—Bovine tubercle of pearl disease.

partly composed of tubercles, the bulk of the diseased area presenting evidences of ordinary or peculiar inflammatory changes to which the presence of the tubercles has stimulated the tissues.

Again, in general lymphatic tuberculosis, one may see diffuse epithelioid and round-cell increase without special arrangement, but displacing or distorting lymph-gland architecture (Fig. 41).

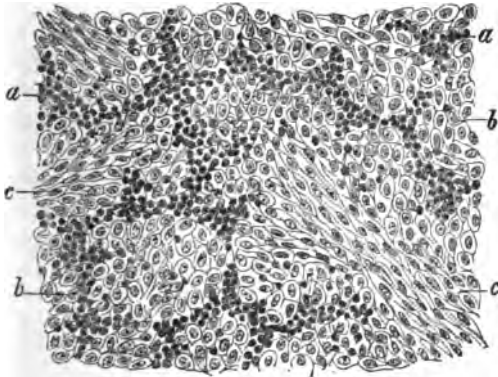


Fig. 41.—Tuberculous lymphatic gland: *a, a*, Lymphadenoid tissue; *b, b*, large round cells (epithelioid); *c, c*, large spindle cells (Ziegler). This is the diffuse form and bears resemblance to Hodgkin's disease.

The tubercle bacilli in the earliest stages of the tubercle may be seen lying in the tissue and perhaps between the epithelioid cells first formed. With the evolution of the disease they are more and more abundant, are largely within the cells, and the giant-cells in particular may contain large numbers (Fig. 42).

As the necrotic changes increase, the bacilli become less conspicuous, and eventually none may be visible. The existence of the bacilli, however, cannot be doubted, since injection of portions of such tubercles produces the disease in guinea-pigs.

Syphilis.—Histology.—In syphilitic processes of all kinds and in all of the stages there is a tendency to accumulation of round cells and proliferation of connective-tissue cells, the processes being first manifest around the smaller blood-vessels, but subsequently extending to other parts of the tissue. The walls of the blood-vessels themselves are frequently involved, and thickening of the inner or of all the coats may be observed. Complete destruction of the vascular channels is not rarely the consequence. Some authors locate the earliest changes in the small veins and lymphatics. In the subsequent course of the disease there is a tendency to the formation of distinct cicatricial connective tissue,

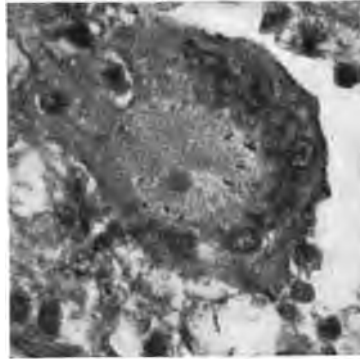


Fig. 42.—Giant-cell containing bacilli (from a photograph made by Dr. William M. Gray).

giving rise to indurated scars, strictures, or diffuse sclerosis; and a less pronounced tendency to the occurrence of degenerations, mucoid and fatty, causing areas of degenerative softening.

The Chancre.—The *initial lesion* first presents small areas of round-cell infiltration in the deeper layers of the skin or mucous membrane and, as a rule, in the neighborhood of the blood-vessels. The connective tissue at the same time undergoes proliferative change, and spindle-shaped cells or irregular embryonal connective-tissue cells are found mingled with the round lymphoid cells, or surrounding foci of the latter. Giant-cells are rarely present. Thickening of the blood-vessels may be observed in the later stages or from the very first. The tissue elements of the skin and of the subcutaneous tissue are usually separated by infiltrating liquid, and the latter may loosen the tissues of the surface and cause exfoliation of the superficial epidermis, and thus lead to the development of the primary vesicle or the erosion so commonly

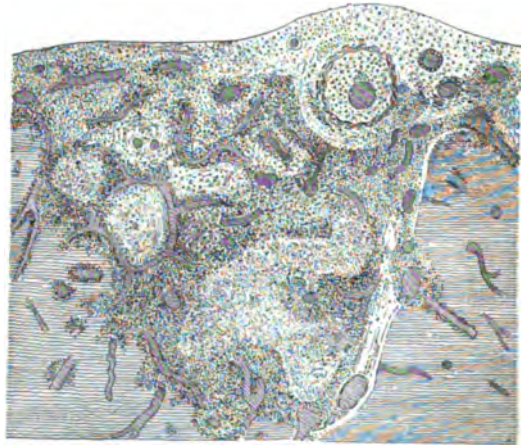


Fig. 43.—Gummatous meningo-encephalitis (Ziegler).

seen. The induration of the chancre is probably the result of the sclerosis of the vessels and the general connective-tissue hyperplasia, as well as in part due to the tense infiltration of serous liquid.

It is characteristic of syphilis that the periarterial change occurs first, to be followed by the parenchymatous. This process may go on during all the secondary stage. Obliterating endarteritis is a type of change in syphilis that may occur at any stage.

The Mucous Patch.—The *condyloma latum* is very similar in structure to the initial lesion. There is, first, round-cell infiltration of the deeper layers of the mucous membrane, with serous exudation and erosion of the surface. Later, there is a tendency to connective-tissue hyperplasia, though this is less marked than in the case of the chancre.

The Tertiary Lesions.—The *gumma* is composed in large part of round cells derived from the blood-vessels and proliferated connective-tissue cells, having a spindle shape or various irregular forms. Epi-

thelioid cells are less abundant, and giant-cells, though occurring at times, are usually few in number. Plasma-cells may be abundant in syphilitic lesions, and mast-cells occur in small numbers. The blood-vessels are nearly always more or less affected, the intima being thickened and the adventitia being also involved to a variable extent. Periarterial changes are very conspicuous. There is some new formation of blood-vessels, the lesion in this respect differing from the nodular lesion of tuberculosis (Fig. 43). Secondary changes are almost always seen in gummata of considerable dimensions, being more diffuse and irregular than in tuberculosis. Among these may be recognized a gradual necrotic transformation of the cells in the center of the lesion, with distinct fatty degeneration or myxomatous change. The degenerated tissue may be infiltrated by leukocytes in a state of fair preservation. The differential diagnosis between a tubercle and a gumma is by no means easy, and there are cases in which it is well nigh impossible. Stains for the bacilli or the spirals should be used.

In the diffuse tertiary lesions of syphilis the tissues of the affected organ are indurated, the connective tissue showing more or less pronounced hyperplasia. These processes cannot be certainly distinguished by their microscopical or general features from sclerosis due to other causes, unless there are associated miliary or massive gummata.

Leprosy.—The nodule or *leproma* is a somewhat indurated growth resembling the tubercle, but differing from it in its greater vascularity and in the absence of the tendency to cheesy necrosis. Microscopically, it is composed very largely of proliferated connective-tissue cells of different forms, plasma-cells, and endothelioid cells. New blood-vessels are discovered in more or less abundance, the newly made tissue following their course, and a tendency to complete organization with the formation of fibrous tissue may be seen in the character of the cells and the presence of fibrous intercellular material. Elastic fibers degenerate. The bacilli occur within the cells and possibly also between them, arranged either singly, in pairs, or in bundles like wrapped-up cigars. They are always found in groups and usually in large numbers. They multiply within the cells, the protoplasm of the latter at the same time undergoing a process of swelling and degeneration. This at first spares the nucleus, but finally the nucleus itself is broken down and the cell is thus converted into a sac containing degenerated protoplasm and abundant bacilli (Fig. 44). The term *lepra cell* has been given to these. The bacilli also occur in the connective-tissue cells, in fatty tissue, and very often in the adventitia of blood-vessels. Giant-cells may be formed, though they are not frequent and are rarely typical, being much vacuolated. In a pure lesion polymorphonuclear cells are usually absent. Secondary infections or injuries may lead to suppurative or

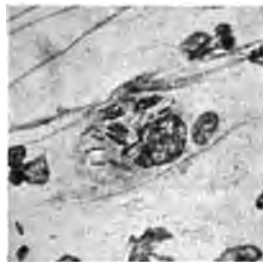


Fig. 44.—Lepra bacilli in a lepra cell (Karg and Schmorl).

other forms of softening, and the final termination, either with or without previous softening, may be cicatrization. In some instances the lesions of the internal organs met with in supposedly leprous cases, notably those of the lungs, intestine, kidney, and serous surfaces, have been found avascular, with more tendency to necrosis and containing more giant-cells; in some of these cases inoculation has shown that the lesions contained tubercle bacilli. Whether these were strictly tubercles, or whether they were lepromata with secondary infection with tubercle bacilli, cannot be decided. They were certainly not pure leprosy, and more probably were purely tuberculous.

The anesthetic areas and pigmented or light colored spots of the anesthetic form present somewhat the same histological features as the leprous nodule, though in a diffuse form. Formerly these lesions were considered entirely the result of trophic changes. In these cases the more conspicuous lesion is that of the nerves. These may show nodular thickening of the perineurium with inflammatory and degenerative changes of the nerve itself. The bacilli are present in these lesions, lying mostly within the cells of the perineurium. The effect is at first to irritate the nerve and later a compression and degeneration of the nerve-fibers. Changes in the spinal cord have occasionally been discovered.

Glanders.—In acute glanders there is a local necrosis of the fixed tissues with a fibrillary or granular degeneration sprinkled with chromatin debris and surrounded by a zone of polynuclear leukocytes. The elastic fibers remain in good condition for some time, but finally swell and degenerate. In chronic glanders the nuclei are retained for some time and the cells present an epithelioid type. Considerable connective tissue is formed. Polynuclear cells, but not typical giant-cells, may be seen.

Actinomycosis.—The first lesion of this infection is a simple suppurative focus. This shortly assumes a tubercle arrangement by the appearance of giant- and epithelioid cells. It, however, soon proceeds to softening and central necrosis. The surrounding tissue is occupied by an active granulation process, losing all specific character except a tendency to fatty degeneration of the cells. The pus contains the sulphur granules of the organism, but the mycelium with its swollen end may be found penetrating the granulation tissue.

The histological changes in other streptothrix infections—mycetoma, pulmonary streptothricosis—are essentially the same.

Rhinoscleroma.—The histological lesions of this condition are usually quite specific, although some authors still express doubt of the etiological importance of the *Bact. rhinoscleromatis*. The specificity of this chronic granulation tissue lies in the large Mikulicz's cells, a form of plasma-cell with hydropic or hyaline degeneration and a relatively small nucleus. They contain the bacilli. (See also page 303.)

Saccharomycosis.—This condition gives rise to nodular necrotic masses surrounded by irregularly placed abundant giant-cells and active connective-tissue formation in the immediate neighborhood. The masses grow actively and may form considerable tumors. The budding

yeasts may be found in the pus and some are seen in the giant-cells. The more acute the process, the more necrotic. Chronic cases tend to show tumefactions.

Sporothricosis.—The peculiarities of this granulation tissue consist in a diffuse growth of epithelioid and plasma-cells and connective tissue. There is no nodular growth. The new growth and its supporting structure do not tend to undergo degeneration.

Mycosis fungoides may be a granuloma. Its exact nature is as yet uncertain. Its discussion is found under the Tumors, p. 199.

REGENERATION

Definition.—The term “regeneration” is applied to the formation of new cells or tissues to take the place of those destroyed. Regeneration may be physiological or pathological. The former is that which occurs in the normal life of the organism and by which the cellular wear and tear is counterbalanced. Pathological regeneration is the more massive and often atypical reconstruction follows disease or injuries. Regeneration is one of the essential elements in inflammation, as has been shown in the preceding pages, but it is not always an inflammatory process.

Etiology.—The cause or mechanism by which normal regeneration is brought about is more or less obscure. The cells have an inherent tendency to multiply, and this goes on to a certain point, at which the normal development is complete. This limit is probably maintained by some restraining influence, but the nature of this is unknown. In the skin and mucous membranes, where physiological regeneration is most active, new cells are constantly produced and the older cast off. In what manner the balance is so maintained that production and destruction keep their equal pace is as yet matter only for speculation. The idea of action and reaction occurs naturally to the mind, and it seems probable that the reproductive processes are dependent in some way upon the loss of substance. In some cases the normal restraining influence seems to be deficient and giant growth results. In all forms of normal or physiological regeneration the reconstructed cells are exactly like the pre-existing cells, and the status of the tissue is unaffected. In highly specialized cells, such as those of the nervous system, regeneration seems to be intracellular—that is, the cells are constantly rejuvenated by supplies of nutriment rather than by reproduction *in toto*. It may be said in general that the lower the type of cell in specialization, the greater its power of self-propagation by cell division. The reverse is likewise true. A cell will also reproduce better when young and in its normal position than otherwise.

In pathological regeneration there seems to be abnormal stimulation of the reproduction of cells as well as a reduced restraint. It is not improbable that various toxic substances have the power of stimulating the formative process, though this has not been actually demonstrated. In all cases in which degeneration is due to mechanical, thermal, or

toxic causes there is, first, destruction of cells, then regeneration. In such cases the relief from the accustomed pressure may serve as a withdrawal of restraint, but at the same time there is doubtless augmented formative energy. In other words, nature repairs defects in excess. The stimulus may be the same agency as that which caused the primary cell destruction, or it may be due to the influence of formative irritants derived from the dying and dead cells. The demonstration that micro-organisms are able to produce substances having a strong attractive or repellant influence upon leukocytes gives some warrant to the belief that similar substances are at work in the regenerative changes that accompany bacterial diseases. In the case of tissue destruction due to other causes similar products possibly play a part. It seems fair to assume from the work of Loeb and Miescher and others that certain conditions involving oversupply of protein and some alterations in chemical reaction in functioning tissues may be sufficient cause for proliferation. If this be true of relatively normal tissues, somewhat similar conditions may play a part in the proliferative changes occurring in pathological states.

Pathological Anatomy.—In the normal regeneration of cells the process is one of gradual *cell multiplication* without marked changes of any sort. Pathological regeneration may be equally simple, but more often there are complicated changes in the pre-existing tissues and new formation of blood-vessels may precede or accompany the regeneration. The vascular regeneration is a necessary preliminary, having the purpose of supplying abundant nutriment to the tissues undergoing proliferation.

Cell multiplication occurs in two ways, the direct and the indirect. The former method is one of simple cleavage, by which the cell is divided into two or more parts. This mode of division is unusual.

Amitosis or *direct cell division* is a retrograde process in every instance. In some cases it is simply a fragmentation of the nucleus owing to altered conditions in the cell and probably not in any sense an attempt at cell division. When numerous fragments are formed, and some growth of the nucleus attends the process, giant-cells may result because the protoplasm does not divide. Evidences of degeneration of the protoplasm are apt to be met with in such cells. Of these, vacuolization, granular or hyaline change, fatty degeneration, and even calcification may occur.

The common method is called *indirect segmentation*, *karyokinesis*, or *karyomitosis*. In this method complicated changes begin in the nucleus and finally lead to division of the cell into two or, rarely, into several parts. It is unnecessary to refer to the histological stages in detail, but in a general way we may describe the process as follows: (1) The nucleus of the cell enlarges and the chromatin fibers become thicker and less closely woven than normally; (2) U-shaped loops of chromatin fibers arrange themselves around a central clear space or *polar field* to form a *mother wreath*; (3) these loops then undergo longitudinal cleavage and the separated parts move one to one pole and the other to the

opposite pole of the cell, forming *daughter stars*, which eventually become coarse and then fine skeins of new nuclei; (4) the protoplasm of the cell finally divides and the process becomes complete.¹

Regeneration of Epithelium.—In its simplest form, as, for instance, after a very slight injury to the cornea, regeneration occurs by a direct replacement of the injured cells by multiplication of the cells of the same kind at the point of injury. The intact cells become somewhat swollen, then undergo ordinary cell division, and new cells are formed. In the reconstruction of surface epithelium involving to some extent the underlying tissues, as in lesions of the mucous membranes or skin, the surface epithelium undergoes the same kind of multiplication as that just described, and the mass of new-formed cells dips down somewhat into the space caused by the injury. In the deeper tissue new formation of connective tissue takes place in the manner already described under the head Healing of Wounds, and to be presently discussed more fully. In the subsequent stages the redundancy of epithelium caused by the dipping down of the mass of new cells into the injured area is reduced by condensation and gradual disappearance of some of the cells, so that eventually the epiderm or the layer of epithelium on the mucous surfaces does not differ from that in the surrounding parts. When large areas of epithelium have been destroyed the replacement of the epithelial covering occurs by gradual increase of the cells at the periphery of the denuded area, until in time the whole surface becomes covered. When skin-grafting is practised by the surgeon, a similar growth of the epithelial cells starts from each of the grafts placed upon the denuded surface. The repair of defects in endothelial surfaces follows the same general laws as lately shown by Carrel. In lymph-vessels the endothelium may regenerate or may possibly be involved in connective-tissue formation.

Regeneration of Fibrous Connective Tissue.—In all cases of extensive injury the connective tissues take an active part in regeneration, and in the case of highly specialized tissues new-formed connective tissue takes the place of the specialized tissue, which itself is less capable of regeneration. There is almost always an excess of cellular reproduction and consequently an enlargement of the part affected by the injury. Subsequently the cells contract, and thus the bulk of the new tissue approximates that destroyed. The new tissue must, of necessity, be more firm, as a larger number of cells are condensed in the space previously occupied by a less number.

The important processes in regeneration of the connective tissues are: swelling and multiplication of the connective-tissue cells, migration of the new cells into the area of injury, and the formation of new

¹ **Abnormal Cell Division.**—There are certain disorders of cell multiplication that may be here described. Karyokinesis, instead of being a regular process of division of the nucleus into two daughter nuclei, may proceed irregularly. Sometimes the process is *asymmetric*, i. e., does not lead to equal division; in other cases it is *multipolar*, several instead of two daughter nuclei resulting. Other less definite irregularities are sometimes observed, and some have held that cell division may occur by a process of mixed karyokinesis and amitosis. It is important to recognize that some of the forms of nuclear degeneration (karyorrhexis, hyperchromatosis) may be mistaken for normal or abnormal karyokinesis. Pathological karyokinesis is most frequently seen in malignant tumors.

blood-vessels. The old connective-tissue cells increase in size and then undergo division by mitosis of the nuclei. As a result, new cells of rounded outline and with rather pale nuclei result. These may remain at the point of their formation or may actively migrate, like leukocytes, toward the center of injury. Subsequently they tend to undergo a change of form, becoming elongated and spindle-shaped or irregular in outline (Fig. 45). It is these cells, and not the polymorphonuclear leukocytes, which are active in the final restoration of the tissues, and the terms "formative cells" and "fibroblasts" are, therefore, appropriate. It is believed by most observers that endothelium can go over into connective tissue. It seems certain that this membrane has something to do with the organization of a thrombus. With continued irritation the cells change from a flat plate to almost a cubic form. When the new cells have been formed, increase of intercellular substance takes place. The fibrils may be derived from the cells themselves by separation of filamentous prolongations growing out from the pointed extremities of the spindle cells, or they may result from a cleavage of a homogeneous intercellular substance in which the cells are at first embedded. This

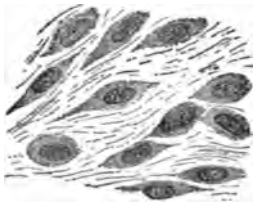


Fig. 45.—Fibroblasts forming fibrous tissue (Ziegler).

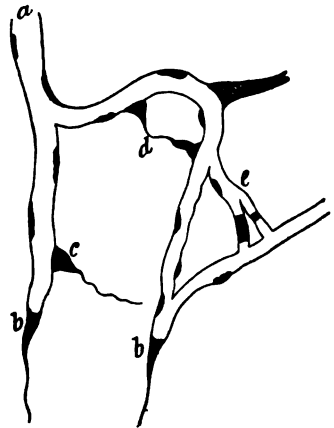


Fig. 46.—Formation of new blood-vessels, as seen in the tail of a tadpole (Arnold).

intercellular substance doubtless is a product or a secretion of the cell. In either case the fibrils are essentially a result of cellular activity. In the later stages of connective-tissue regeneration the fibrils contract, and the tissue thus becomes more compact, especially when the amount of intercellular substance is excessive. Collagen and fibroglia fibrils are reproduced and at some places also elastic fibers. The cells at the same time decrease in size and some are so compressed as to be almost obliterated. It is characteristic of new-formed connective tissue, however, that up to the latest stages the tissue is more cellular than normal tissue.

According to Marchand three forms of round or lymphoid cells are also represented in connective-tissue regeneration: one the small lymph-cell, and two called leukocytoid cells. One of the two is somewhat larger than the small lymph-cell, possessing a relatively pale staining nucleus, and considerable slightly granular or vacuolated protoplasm. This is the *polyblast* of Maximow and it may come from the blood-

stream or the tissue cells. The third variety is the *plasma-cell*, which has been described on p. 122.

Giant-cells of the foreign body or proliferative type are common in regeneration, and they act as phagocytes to remove substances which are not dissolved.

New formation of blood-vessels is an important factor in regeneration of connective tissue when the extent of injury has been considerable. Repair of very trifling injuries, such as an incised wound followed by a close apposition of the injured surfaces, does not involve any new formation of blood-vessels, though the pre-existing vessels become somewhat hyperemic. When the injury is more extensive, vascularization is a necessary step in the repair. The new vessels result from extensions from the pre-existing vessels (Fig. 46). The endothelium of the capillaries becomes swollen and here and there processes are sent outward. These may unite with similar processes from adjacent capillaries or from the same one at a point somewhat distant, and central vacuolization may convert the loop into a primitive channel which eventually becomes a fully formed capillary by multiplication of the endothelial nuclei and formation of definite endothelial cells. Sometimes the new vessel is formed by parallel outgrowths from adjacent endothelial cells of the parent capillary, leaving a space between the new-formed cellular extensions. Such new vessels occur around the site of injury and project in the form of loops into the area of injury itself, being surrounded by the new-formed connective-tissue cells above described. Usually the area of injury is first filled with a blood-clot or coagulated exudate derived from the injured tissues. This forms a matrix in which the new-formed connective-tissue cells migrate and the capillary loops project. The clot or coagulated exudate is subsequently absorbed as the process of cellular replacement advances. The young connective tissue thus formed later contracts and the small blood-vessels are largely reduced by compression, so that the appearance of the tissue may become that of a quite avascular structure.

In regeneration of connective tissues, elastic fibers are not observed in the earlier stages. Subsequently they are formed more or less abundantly.

Regeneration of cartilage and bone takes its origin from the perichondrium in the former case and from the periosteum or marrow in the latter. The process begins as a proliferation of chondroblasts or osteoblasts respectively, which have the power to lay down a matrix which attracts chondromucin or bone-salts, as the case may be. The adult bone and cartilage cells have not the power to regenerate. In both instances embryonal connective tissue, such as that which occurs in regeneration of fibrous connective tissues, is first formed. Later, in the case of cartilage, areas of homogeneous intercellular substance appear, and thus cartilaginous substance is developed. Very commonly, however, regeneration of fractures of cartilages is mainly fibrous, and there may be little if any true cartilage. Regeneration of bone in the case of fractures proceeds in much the same fashion, an abundance of cellular

tissue first appearing around the fractured ends of the bone, within the marrow cavity at the point of fracture, and between the broken ends of the bone. In this embryonal connective tissue branching and radiating columns of rudimentary osseous tissue appear as a sort of network in which complete ossification occurs at subsequent stages. Later, much or all of the embryonal tissue around the fracture and within the marrow cavity is absorbed, and the repair of the fracture is made complete by thorough ossification of the part between the ends of the bone. When bone-salt deposit is deficient, cartilaginous union results.

Regeneration of adipose tissue begins with a formation of fat-free cellular tissue. Later the cells become infiltrated with fat.

Regeneration of Muscle Tissue.—Striated muscle after injury or excision is capable of some regeneration by, as a rule, amitotic multiplication of the muscle nuclei. The area of destruction if considerable is first occupied by regenerating connective tissue into which irregular protoplasmic projections from the ends of the divided muscle-fibers extend. Subsequently these elongate and form new muscle-fibers, but they are apt to be narrow and more or less irregularly arranged, so that the regeneration is rarely complete.

Regeneration of smooth muscle by mitosis takes place in some cases (uterus), but connective-tissue formation occurs instead when the areas of destruction are large.

Regeneration of Glandular Organs.—In epithelial glandular organs, such as the liver, kidney, mammary or salivary glands, considerable new formation of epithelial cells may take place. It has been taught that gland cells are replaced by tissue cells below the basement-membrane. This is undoubtedly incorrect. Glandular cells are recruited from glandular cells or occasionally from the cells of small ducts. In the liver there may be active proliferation of cells and formation of new biliary ducts. This is seen in experimental injuries and also in association with some forms of cirrhosis. In the case of the kidney, regeneration may occur in the cells of the straight tubules, while in the mammary glands, salivary glands, and the smaller glands of mucous membranes new formation of acini and ducts proceeds from the smaller excretory ducts of the affected glands. In this way an atypical glandular structure may result. This will be discussed under Adenoma. Skin glands and their outlets are regenerated if the fundal parts have not been destroyed by the surface damage.

Regeneration of Nervous Tissue.—Nerve-fibers are capable of considerable regeneration, which proceeds from the sheath of Schwann. The medullary substance is differentiated within the sheath, and the new axis-cylinder is an outgrowth from the existing axis-cylinder or the nerve-cell. Regeneration of the nervous fibers in the brain and cord takes place to but a slight extent. Injuries here are usually repaired by the formation of new connective tissue and regenerating glia. The large multipolar nerve-cells seem to be capable of intracellular repair after partial injuries, but complete regeneration is never accomplished. It is possible, however, that they may be capable of

limited proliferation, as such cells occur in certain tumors. Neuroglia proliferates, but less readily than fibrous tissue.

Pathological Physiology.—Regeneration is the more or less effective effort of nature to replace injured or excised tissue. The restoration is complete in proportion as the tissues lack in higher organization and differentiation. The younger the individual, the more complete the regeneration of his tissues; and the lower the type of tissue, the more complete will be its restoration. In glandular organs, though some proliferation of epithelial structures occurs, the new-formed glandular elements are but little capable of glandular activity. Newly developed nervous tissue is least capable of restoring the original function.

METAPLASIA

This is the term applied to the transformation of one form of tissue into another without the intervention of a stage of regeneration by cellular multiplication. It is exemplified under normal conditions by the transformation of cartilage into bone. It occurs with great frequency under pathological conditions, and may be here described as a collateral or inferior specialization in a tissue of the same original character, for mutations of tissue types do not occur. Thus, cartilaginous tissue may have an abnormal deposit of bony salts, fibrous tissue may become bony or fatty or myxomatous, but these never become glandular structures, nor does gland tissue ever become nervous tissue. The process may be a purely interstitial affair and the cells suffer secondary changes. In other cases of metaplasia the cells may be primarily altered, as when ordinary connective tissue is changed to fatty tissue.

The process, except where accommodative or defensive, is not easily understood. Cells of the embryo destined to be epithelium are differentiated so that they may assume their adult normal form and function; by metaplasia one type of epithelium may adopt the form and at times the function of another. The same facts are true for connective-tissue cells. Fully differentiated fibrous tissue may become calcareous without the agency of osteoblasts from bones, connective-tissue cells acting the rôle of the latter.

Although it has been claimed that fat cells are descended from the mucoid embryonal cells, some observers seem to think that connective-tissue cells not descendants of these fetal elements may become fat cells by metaplasia.

The metaplasia of epithelial cells, as, for example, a change from cylindrical to squamous cells on the surface of mucous membranes, has been doubted by some authorities. They assume that such apparent transformations are due either to ingrowths of the new order of cells from surrounding areas or by enlargements of islets of mucosa covered with such cells. Experiments, as those of Fütterer, however, indicate that metaplasia does occur. In this process not only the old epithelia are altered by the changed conditions, but the new-formed epithelia, under the altered conditions of environment, develop into the new order of cells rather than into the parent form.

The causes of metaplasia are, naturally, changes in physical relations, including alterations of pressure and irritation, carrying with them some differentiation of function and changes in nutrition. Injury or chronic irritation may bring these factors into play. Examples of metaplasia are to be found in the change of the bladder epithelium to a horny layer from a calculus; the flattening of the bronchial epithelium in bronchiectasis; the appearance of calcareous deposits in chronically inflamed connective tissues, especially around joints. Changes similar to these repeatedly occur in neoplasms.

The term *retrograde change* (Ribbert) has been applied to an alteration of cells in which under pathological conditions a lower order of differentiation is assumed, but in which the new order of cells do not acquire specific characteristics of a different sort. Thus, cylindrical epithelia of glandular tubules may be changed to cuboid cells lacking the original functional characters and not possessed of a new function such as would be the case with squamous cells. Similarly, in the atrophy of striped muscle, non-striated, narrow fibers with abundance of nuclei give evidence of a retrograde change toward embryonal conditions.

CHAPTER VI

PROGRESSIVE TISSUE CHANGES

THIS term may be used to designate pathological conditions in which there is a tendency to the formation of new and functionally active tissue.

HYPERTROPHY

Definition.—The term “hypertrophy” is applied to a pathological condition in which a certain part increases beyond the normal size, without marked alterations from the normal structure. The term hypertrophy is frequently used loosely to designate enlargements of various kinds in which but one tissue of an organ is increased, or in which there is deposit of abnormal exudate. Such instances are not, strictly speaking, cases of hypertrophy.

Etiology.—The causes of hypertrophy are quite numerous. In some cases there is a distinct increase of functional demand brought about in some way or other, as in the hypertrophy of the muscles of athletes; in the hypertrophy of a kidney after disease or removal of its fellow; or in the hypertrophy of a limb after injury to the opposite limb. The direct increased demand for work occasions the hypertrophy. Sometimes there appears to be a special tendency to hypertrophy, as is evidenced by the occurrence of congenital or hereditary giant growth. Most of these, however, are instances of peculiar and abnormal development, rather than of hypertrophy, the latter being a condition developed pathologically in parts previously well formed. Disturbances of the nervous system and internal secretions may play a part in the development of some hypertrophies, but these influences are obscure. Continued congestion undoubtedly stimulates tissue growth, but this element is the means whereby hypertrophy is effected rather than the original cause.

In the compensatory or vicarious functional hypertrophies we must assume that two factors are at work—first, the stimuli resulting from increased demand, and second, the adaptive mechanism of the part adjusting reaction to stimulation. It may be further assumed that there is always a margin of safety between the work thrown upon a part and the limit of work possible. During continued activity the cell enlarges, for which it must have increased nutrition and some period of rest. Should the stimulation continue without rest and increased nutrition, degeneration may occur.

Some of the hypertrophies, such as that of the breast during pregnancy and lactation, are undoubtedly due to internal secretions, probably of ferment nature. The *hormones* belong to this class. We may also

include in a similar group the growth taken on by some organs, like hair-follicles and mammae, at puberty. Derangements of the ductless glands may lead to hypertrophies, among which the most conspicuous example is acromegaly from disease of the hypophysis.

Pathological Anatomy.—Parts the seat of genuine hypertrophy are uniformly increased in size. This is well seen in the condition termed "giant growth," or "gigantism," in which the bony framework and other tissues may be uniformly affected, the individual growing to excessive size. Sometimes local giant growth of the skeleton and external tissues is observed, as in the case of one member or a single finger. This has often been found in corresponding members on the two sides of the body. In certain cases termed "hypertrophy," in which this designation is more or less justified, lack of uniformity in the increase of the organ or part affected causes irregular increase in size. Hypertrophy and hyperplasia may be used by the economy to make up loss of bulk the result of disease.

Histologically, hypertrophy may be *simple* or *true hypertrophy*, and *numerical* (hyperplasia). In the former there is increase in the size of the individual cells; in the latter the cells increase in number, though the individuals are not excessive in size, and, indeed, often smaller than the normal cells. In the hypertrophy of the uterus during pregnancy and of the heart muscle in compensatory enlargement, simple hypertrophy predominates. Hyperplasia is very commonly a factor in hypertrophy of any kind, but may be so strictly limited to one tissue of an organ, notably the connective tissue, that the term "hypertrophy" is in no way applicable. Between these extremes there are all grades of cases, in many of which it is difficult to determine whether the designation hypertrophy is applicable or not. In some cases the clinical designation *hypertrophic enlargement* is used, though the condition is strictly one of hyperplasia of the connective tissue, with a tendency rather to atrophy than hypertrophy of the proper substance of the organ. Instances of this are hypertrophic cirrhosis of the liver, some cases of hypertrophy of the heart muscle, etc.

Pathological Physiology.—Hypertrophy results from an increased demand upon an organ or member, and leads to increased functional capacity. Thus, in the case of a diseased kidney, the opposite kidney may be capable of compensating for the deficiency; in the case of laborers the enlarged muscles may meet every demand made upon them. There are occasional instances of more or less genuine hypertrophy resulting from diseased conditions, in which the excessive functional capacity causes marked disturbances, as, for example, in case of enlargement of the thyroid gland.

TUMORS

Synonyms.—New Growth, Neoplasm, Pseudoplasm.

Definition.—In its broadest etymological significance the term "tumor" designates an abnormal swelling in any part of the body. This definition, however, is not applicable to tumors in the ordinary sense.

Inflammatory growths and collections, such as abscesses, hyperplastic deposits, and the like, are excluded. Pathologists, however, have always found it difficult to construct an accurate definition for tumors or to draw sharp lines of separation between them and the inflammatory or infectious swellings that occur in various diseased conditions. An attempt to establish an ultimate boundary-line is evidenced by the term *autonomous new growths*, applied by Thoma. This name is used to designate the supposed spontaneous origin of new growths and their independence of ordinary causes, such as are recognized in the production of inflammatory outgrowths and the like. It cannot be said, however, that tumors are causeless, and in the discussion of the etiology we shall have occasion to refer to certain definite factors known to aid in their production. It is true, however, that the growth of tumors is practically always out of proportion to the amount of local irritation or to the severity of other factors that may be conceived as playing some part in the etiology; and in the great majority of cases the causes, whatever they may be, are obscure or unknown. A negative definition perhaps best suits for the delimitation of this term "tumor." Thus, we may exclude from the category of tumors all swellings in which some sufficient cause is discoverable, and include the apparently causeless growths among the true tumors. A further characteristic of tumors is their independence. Excepting the blood-supply, there seems to be no dependence on the organism in which they occur, and they contribute nothing to the continuance of its life and its integrity. Nor is there any apparent restraint to the indefinite growth of the tumor comparable to that which keeps normal growth and even pathological processes of other kinds within certain bounds.

Despite all of these characteristics, there are cases in which pathologists cannot determine positively whether certain growths are to be classified as tumors or some other conditions.

Etiology.—A great number of theories have been suggested to explain the causation of tumors.

Among the older writers there was a disposition to attribute the occurrence of tumors to a *constitutional dyscrasia*, or a diseased state of the fluids of the body, a cause as obscure as the tumor.

Recently a number of more elaborate theories have been constructed that resemble this older one, in ascribing the growths to some form of disturbance of vital activity and of cell proliferation, without explaining the cause of such disturbance. For example, we may refer to the theory that tumors result from a retrograde change in vital properties of certain cells, so that they tend toward the original characteristics of the germ-cells and multiply in a purposeless and indeterminate manner. This theory was based upon the fact that asymmetrical karyomitosis is frequently observed in tumors. It was assumed that in this unequal division of the cells the peculiar, differentiating qualities of the cell are cast off with the smaller portion, causing the larger, in the course of several generations, to become *anaplastic* or retrograded. It has, however, been shown that the same sort of asymmetrical mitosis also

occurs in non-tumorous conditions; and an additional factor that must enter into the theory, the nature of the stimulus that causes the anaplastic cells to proliferate actively, is wholly unexplained.

According to the late observations by Slye upon mouse tumors, neoplasms represent "a manner of growth" transmissible to progeny in a Mendelian sense, the faulty character being dominant or recessive, so that by proper mating it can be made to remain a dominant inherited feature or to die out.

Another theory would explain the occurrence of new growths somewhat upon the basis of infection, assuming, instead of an exogenous infection with micro-organisms, an endogenous infection. This was suggested by the discovery of leukocytes within the tumor-cells. The author of this theory explains that in consequence of some thermic, chemical, or other irritation certain cells may become, so to speak, infectious, assuming the rôle of a sperm-cell and stimulating the adjacent cells to abnormal multiplication. Such theories, however, are entirely speculative, and leave the etiology as little settled as before.

Virchow strongly advocated the theory of *external irritation*, and was able to cite numerous examples of tumors that had arisen in consequence of more or less definite traumatism. Thus, in cases of carcinoma of the breast, in the epithelioma occurring on the lips in pipe-smokers, and in the epithelioma of chimney-sweeps, there is at times a definite history of unusual irritation, and the relation of cause and effect seems easily traceable. It must be admitted, however, that there is some further underlying cause which renders one individual liable to tumor growth, while another is not thus predisposed, and though it is probable that some tumors owe their origin to irritation as the exciting cause, all cases cannot be thus explained.

Cohnheim advanced the interesting theory that *defective development* lies at the basis of tumor formation. According to his theory, there are frequently small errors of development leading to the inclusion or misplacement of portions of the original blastoderm in the midst of tissues derived from a different layer of the embryo. These inclusions, or *embryonic rests*, are independent of the function of the part in which they lie, and are assumed to be liable to subsequent sprouting, with the consequent formation of tumors. There is evidence that this theory contains a certain measure of truth, and some tumors, as, for example, certain ovarian growths, tumors of the parotid region, and others, seem to originate in this way. The theory, however, is not by any means universally applicable, and it leaves unexplained the final proliferation of the embryonal rests that had previously remained dormant. The assumption, however, that such rests would quite readily take on active growth as a result of various simple irritations, or when the vitality of the part was stimulated, is less forced than that which would attribute such proliferative activity to cells in their normal relation to surrounding tissues. Similar conditions may be brought about by disease or injury of various tissues. This is the essence of Ribbert's "disturbance of tissue tension" theory. If certain cells or parts of the tissue are displaced

from their normal relations to the surrounding structures, the same conditions are established as by the embryonal displacement of portions of tissue. Not improbably this sometimes occurs either as a result of accident or of disease, and subsequently the displaced portions may prove the starting-point of tumor growth. Some authorities have insisted upon this as a frequent occurrence and as explanatory of many tumors. Experiments have shown that certain types of epithelium (epidermis), both adult and fetal, as well as certain fetal connective tissues (cartilage), may be experimentally removed from their normal position and implanted in another part of the same animal and still retain their potentiality of growth. Such transplanted fetal tissues do not continue to reproduce the fetal stage, but tend to reproduce the ultimate stage of the transplanted tissue. Furthermore, in no case has there been found any infiltration of surrounding tissues by transplanted tissue, nor any tendency to metastasis. All of this shows that there is something additional in the development of tumors beyond the mere dissociation of structures from the surrounding tissues.

Hansemann's theory, based upon the defective mitotic figures seen in tumors, assumes that this want of normality causes the cell function to be disturbed and it fails to undergo its proper specialization (*anaplasia*), so that it becomes parasitic; it is itself the parasite. Oertel also assumes the primary change to be in the nucleus, there being a removal of part of the chromatin. Adami's modification of Hauser's theory assumes that the cell which started the growth lost its specialization, but not its power of reproduction. The relief of other demands upon it permitted the cell to apply all its energy to the dominant remaining function and acquire the habit of growth. This theory is at least consistent with our knowledge that a tumor serves no useful purpose to the body. Yet it must not be forgotten that as far as we know tumor-cells are nourished and have a cell chemistry closely like normal cells. They are at least dependent upon the same pabulum, although the end-products may be different.

Recently an *infectious character* has been ascribed to malignant and benign growths, and there is no doubt that in certain respects tumors resemble infectious processes of definitely ascertained kinds. Their effect upon the general health and their tendency to metastasis are very significant facts. Furthermore, the discovery that various pathological processes characterized by nodule formations resembling tumors in gross appearance are, in reality, infectious growths lends color to the suspicion. The resemblance of such growths to tumors is, however, merely superficial. As far as metastasis is concerned, tumors differ notably from infections, for, in the former, parts of the growth itself are conveyed to some place at a distance from the starting-point, there to proliferate and occasion a metastatic nodule; while in the case of infections the micro-organisms alone are carried to the secondary situation, where they occasion changes *in the local cells* similar to those found in the original focus.

Numerous investigations have been made to determine a possible

connection of bacteria with tumors. These have proved beyond doubt that no bacterium of ordinary sort has any such relation. The possibility of ultramicroscopical organisms and even of such as, through excessive parasitic character, could not live except within cell hosts, has been considered.

Secondary and accidental invasions of bacteria into tumors may occur, and sometimes confusion has been occasioned by this circumstance.

Various investigators since Hanau have found it possible to transplant certain tumors from man to animals or from one animal to another. This has sometimes been interpreted as an evidence of the infectiousness of tumors, though with doubtful propriety, since the transplantation of the tissue from one site to another, like the phenomenon of metastasis, proves only the proliferative tendency of the cells of the growth and not, of necessity, any infectious origin. The transplantation of part of the tumor from one animal to another or from one part to another in the same animal does not differ from the transference of portions of the tumor to distant places in ordinary metastasis.

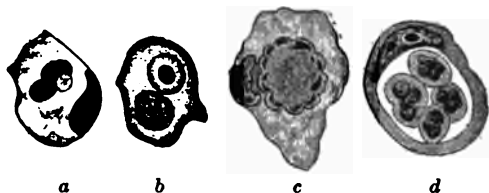


Fig. 47.—Inclusions in cancer cells: *a* and *b*, early stages of "parasitic" bodies; *c*, late stages, showing division by segmentation; *d*, cancer cell containing leukocytes (Ruffer).

The experiments of Rous have shown that certain tumors of the fowl may be transmitted to a susceptible bird by suspensions of cells or a filtrate from this suspension which has been passed through a porcelain filter that would hold back bacteria. He assumes that for these tumors there is a *contagium vivum*. These viruses only produce the kind of tumor from which they come.

In carcinomata and other epithelial new growths, as well as in sarcomata, certain forms of supposed animal parasites have been described. In 1889 Thoma found in the protoplasm and nuclei of carcinoma cells bodies which he regarded as coccidia; and about the same time Malassez and Albarran found similar structures in the cells of an epithelioma of the maxilla. Darrier found bodies of the same kind in Paget's disease of the nipple, and many subsequent investigators have described similar formations. Among these supposed protozoan organisms some are *intranuclear*, some *extranuclear*, and some wholly *extracellular*.

All sorts of bodies have been described in tumors, and to them their respective observers have clung tenaciously as the cause of neoplasms. They have no relation to the causation of tumors, for they have not withstood close investigation. Figures 47 and 48 show some of those de-

scribed. Members of many protozoal and arthropodal genera have been described, even to as large a parasite as *Sarcoptes*. Many of the smaller ones were doubtless artefacts or can be ascribed to the Chlamydozoa of Prowaczek. The larger ones were artefacts or accidental inclusions. We may still learn that such protozoan or metazoan organisms have something to do with neoplasms, judging from Fibiger's results, but we are not yet prepared to accept any of them as the cause.

Recently blastomycetes have been thought of some etiological importance in the causation of carcinoma, but a careful review of the literature is convincing that the evidence does not suffice to establish any such connection. Blastomycetes do not constantly occur in malignant tumors, and when present are not in such numbers or in such relation to the tissue as to establish an etiological significance. The lesions definitely known to be due to blastomycetes are of entirely different character from those of tumor growths, being strictly exudative and inflammatory, with proliferation of endothelium and connective tissue, such as occurs in infectious inflammations. The proliferation of epiderm seen in the blastomycetic skin lesions of man is entirely secondary to the chronic inflammation of the underlying tissues. The latest important communication upon the relation of organized bodies and new growth comes from J. Fibiger, who found nematodes in a papillomatous glandular gastric cancer of wild rats. These nematodes are carried by the roach, *Periplaneta americana*, and can be transferred to unaffected rats, when, if the animal be susceptible (not all are), a carcinoma of constant type will be produced.

Predisposing Conditions.—Whatever may eventually prove to be the immediate cause of tumors, it is certain that predisposing causes are often of great importance. The occurrence of certain forms of tumors in persons of advanced age and in persons whose vitality has been reduced by disease gives evidence that a constitutional predisposition is sometimes requisite for the formation of the new growth. The nature of this vital defect has sometimes been speculated upon, and retrograde vital metamorphosis of the cells or other like changes have been assumed to occur. These theories, however, are purely speculative. In some cases there is evidence of a family predisposition, and heredity was formerly regarded as of great importance. While this element cannot be entirely denied, it has certainly been overestimated.

The Structure of Tumors.—In their histological structure tumors do not differ absolutely from healthy tissues. In all cases they conform more or less with the structure of some one or more tissues. The cells composing tumors invariably represent some one or several types of normal cells, though they may differ in being larger or smaller than the normal cells, or in being of embryonal or undeveloped character.



Fig. 48.—*Rhopaloecephalus carcinomatosus* (Korotneff).

It may be said that the tissue from which a tumor arises is reverting to a state from which perfect differentiation into the normal adult structures cannot or does not occur. They have not lost all differentiation or specialization, since glandular tissue will always produce tumors with a glandular basis, but what is lost keeps the tissues near the parent or embryonal cell type.

Not infrequently asymmetrical and otherwise abnormal mitosis of the cells is observed. Some reference to the varieties of such mitoses will be found in the section on Cellular Necrosis (p. 104). It is important to note that such mitoses are not confined to tumors, but occasionally occur in inflammatory and infectious cellular proliferations.

In the arrangement of their cells tumors differ greatly from normal tissues, and they may be described as being atypical proliferations as far as their organic or tissue arrangement is concerned. The orderly disposition of cells and stroma or intercellular substance seen in the normal tissues and organs is wanting, particularly in the tumors in which organic arrangement is simulated. There may be in some cases entirely typical glandular acini, but the relation of these to each other and the absence of regularly disposed excretory ducts render the tissue, as a whole, atypical.

In the histological examination of tumors it is customary to find scattered through the stroma and between the tumor cells various forms of leukocytes, especially the polymorphonuclear forms and lymphocytes. The imperfect development of the walls of blood-vessels of tumors permits of ready emigration of leukocytes, and there is, therefore, in practically every tumor a certain amount of leukocytic infiltration. Sometimes leukocytes are found in enormous numbers; and when a tumor undergoes inflammatory change, massive accumulations and abscess formations may be met with. Plasma-cells, which are probably altered lymphocytes, are sometimes conspicuous, and mast-cells (basophilic granular cells of doubtful significance) are sometimes found in benign as well as in malignant tumors. They are frequently abundant near the edges of the growth. Eosinophilic leukocytes are occasionally quite numerous. The leukocytes are often found within the tumor cells in the form of inclusions. These, doubtless, have been mistaken for parasites in some instances.

The blood-vessels of tumors have comparatively fragile and poorly developed walls. In the malignant growths or rapidly developing tumors of any sort the vessels are mere spaces between the tumor cells, with little attempt at the development of firm walls. Tumors do not appear to have special nerves. Lymph-vessels are variable. In some they are well developed, having been included and modified from pre-existing ones; in others they are entirely lacking.

Regenerative changes are constantly met with in tumors. In this way the connective-tissue framework of the growth is formed just as such tissue is normally produced, and in this process elastic as well as ordinary connective tissue may be formed. In rapidly growing malignant tumor the framework of the tumor is, for the greatest part, derived

from the pre-existing connective tissue of the affected part, and only in very small measure from regeneration of connective tissue.

The structure of tumors is always closely related to that of the tissue from which it springs, a primary tumor invariably growing in a part in which there is tissue of the type simulated by the tumor, and it is from this tissue, doubtless, that the tumor takes its origin. A connective-tissue growth invariably springs from a part in which connective tissue of some form has pre-existed, and epithelial growths, from a part in which there has been epithelium. Transformation of one variety of tissue into another variety, with the production of a heterologous tumor, does not occur. This statement, though applicable also to secondary tumors, is sometimes difficult of demonstration from the fact that the secondary growths take origin from cells transported to the seat of the metastatic growth, though not normally found in the part in which the secondary tumors have arisen. The occasional discovery of a primary tumor in a locality in which the form of tissue composing the tumor does not occur may be explained upon the assumption (based on some actual demonstrations) that embryonic rests had been deposited at the seat of the tumor by faulty development.

The Shape of Tumors.—This depends to a large extent upon their manner of growth, their situation, and the influence of surrounding parts. We may distinguish, first of all, between *circumscribed* and *infiltrating* growths. The former may be of various shapes, but are distinguished by their sharp delimitation and often by the existence of a distinct capsule; the latter are indeterminate, and the extent to which they involve the healthy tissues cannot be accurately determined. Circumscribed tumors usually grow centrally or in an expansive manner, the new cells being produced in the interior and gradually pushing the older parts outward toward the surrounding tissues. The infiltrating growths are eccentric in development, and may result from a gradual extension of parts of the periphery of the original growth, or by the development of secondary nodules in the neighborhood which become confluent with the original mass. Of the circumscribed growths, we may distinguish small nodules of spherical or ovoid form buried in the substance of the tissue or projecting from some surface as more or less hemispherical elevations. These may be large or small, and the terms *miliary*, *tubercular*, *nodular*, and the like are employed to designate the individual grades. When a tumor projects from the surface in such a manner that the projecting part is larger than the part between the projection and the surface of the body or the organ involved, the term *fungiform* or *fungoid* tumor may be applied, while in the cases in which the new growth is attached by a more or less narrow pedicle the name *polyp* or *polypoid tumor* is applicable. Wart-like growths are known as *verrucose* or *papillary* tumors, and those in which a distinct cauliflower form is developed are called *dendritic*.

The Number of Tumors.—*Primary tumors* are usually solitary at their onset, though examples of multiple primary growths, such as carcinoma involving both breasts simultaneously, or simultaneous

appearance of carcinomata or sarcomata in different parts of the mucous membrane or elsewhere, may be observed. In these cases it is often likely that there was a single tumor at the very onset, with secondary growths originating before the primary growth had reached any considerable magnitude. Primary benign tumors are usually solitary, but sometimes may be found in considerable number, and there may be enormous numbers scattered in various parts of the body. Thus, in cases of multiple enchondromata or multiple fibromata the number may, from the first, be very great.

Secondary tumors are usually multiple. In most cases the number of nodules found postmortem or during life is considerable, and sometimes they are so numerous that large portions of the body may be literally studded with new growths. This is seen very well in the secondary sarcomatous or carcinomatous nodules involving the peritoneum and the other serous surfaces, in which cases the degree of involvement is equalled only by that seen in miliary tuberculosis.

The rate of growth of tumors is extremely variable. Those in or consisting of dense tissue tend to grow slowly, while those of more cellular nature in looser parts grow more rapidly. There may be periods of entire cessation of growth. No rule can be laid down for any group of new growths.

Instances of multiple primary tumors of different kinds are on record. For example, carcinoma and sarcoma may occur in the same individual as can epithelioma and adenoma.

Pathological Physiology.—In most cases tumors take no part in the functional life of the part in which they occur or of the individual. What influence they may bear to the general metabolism is as yet practically unknown. Cases, however, are recorded in which large lipomatous or other tumors have been found to suffer practically no change, while the individual in whom they occurred was undergoing progressive emaciation from starvation. That there is a certain amount of function, however, in some cases is shown by the fact that biliary pigment is detected in the cells in certain carcinomatous tumors of the liver, or abortive milk formation in cancers of the breast. It may be that the want of proper organic arrangement, and particularly the lack of excretory ducts, accounts for the lack of function; but, whatever the cause, it is certain that, as a rule, the functional activity is practically *nil*, or at all events perverted. The occurrence of large quantities of glycogen in certain tumors is perhaps of interest as indicating an attempt at functional activity, but is more probably significant only of active proliferation. With very few exceptions it may be said that tumors are entirely parasitic, living at the expense of the organism and contributing nothing to its development or nutrition.

Certain tumors disturb the general health. This result may be due to secondary degenerative or inflammatory changes dependent upon lack of nutrition or upon irritation and bacterial infection. The progressive cachexia of carcinoma is still unexplained, though in some cases hemorrhage and interference with organic function play a part.

The chemical constitution of tumors and the relation this bears to the body in general and to the changes in body fluids are subjects that have had very important advances in the past few years. They have led to better understanding of the place of a tumor in the body, if not to its etiology. As has been said, the chemistry of tumors is closely like that of the tissue from which they spring. This is also true of metastases. There has been no isolation from tumors of substances that are peculiar to them in general or to any particular variety. Because of their high cell content some tumors contain much nucleoprotein, but this will vary as the parent tissue varies. The digestion products of these proteins are abundant because autolysis is active within tumors. Glycogen also accumulates in tumors because of lowered cellular activity. It is, of course, in highest amount in tumors, the original tissues of which naturally store it. Enzymes of the parent cells are retained in neoplasms.

The inorganic elements are present in the proportion of the proteins that they help to form, and not specifically otherwise.

Enzymes are said to be more abundant in tumors than in normal tissues, and the extensive autolysis of new growths certainly bears this out. Some observers assert that the ferments are different or peculiar to tumors, but this is not proved. Tryptic action is very prominent; so much so, indeed, that carcinoma patients develop a high antitryptic power in the blood. Many tumors have the power of continuing the natural internal secretions of the parent tissue. Thus, thyroid and adrenal tumors and their metastases may produce colloid and epinephrin respectively.

It may be that the cachexia of cancer patients is due to a constant dissemination of the products of autolysis.

Some of the products of tumor growth and extracts of the new tissue have hemolytic properties, but the exact relation of this power to anemia and cachexia is not understood. Metabolism is essentially the same as in wasting disease in general, there being an excessive excretion of protein degradation products and mineral salts except the chlorids.

Tumors fail to set up any constant immune bodies that protect the system against them. The normal blood has a low anticancer-cell power and blood-serum of cancer patients has a lower value. Immunity tests, such as complement fixation and precipitation, are sometimes present, but too variable to permit any conclusions as to their value for diagnosis or relation to etiology.

Tumors may be classified as *benign* or *malignant*. The former do not affect the general health of the patient in any notable degree, and are dangerous mainly by reason of the pressure they may exert on vital structures or the secondary changes (hemorrhages, softening, suppuration) to which they are liable. Malignant tumors generally disturb the general health from the first, and, in addition, tend to recur after removal and spread to other parts of the body (by direct invasion or by metastasis through the circulation or lymphatic channels).

Metastasis, or the transplantation of a tumor from one part of the

body to another, may occur in several ways. The growth may invade surrounding lymphatic or venous channels, and extend in a linear manner sometimes to considerable distances. Thus, a growth of the neck may extend in the jugular vein and vena cava as far as the right heart. More commonly, single tumor cells or small numbers are carried as emboli along the lymphatic or venous channels to some new location, where a secondary growth results. Some tumor cells, especially of the connective-tissue type, are said to be capable of independent ameboid movement; this would favor penetration into capillaries. A third method is that in which parts of the tumor are spread over free surfaces, such as the peritoneum or pleura, and thus occasion new foci. Sometimes, though rarely, this happens on mucous surfaces also.

Occasionally tumors that are ordinarily benign recur after removal or cause metastasis. The former circumstance is not infrequent in the case of nasal polypi and keloids of the skin; the latter in the case of adenomata of the thyroid gland, chondromata, leiomyomata, hemangiomas, and occasionally some others. The manner of growth (central proliferation) doubtless accounts for the infrequency of metastasis of benign tumors.

Tumors have been known to disappear spontaneously. This is rare in human beings, but is commoner in animals suffering from either spontaneous or experimental tumors. The cause is not known. Tumor cells are susceptible to mechanical influences when directly applied. They are more susceptible to x-rays and direct sunlight than normal cells. These agents destroy the vital ferments, but not the autolytic ones. Pressure upon and injury to a tumor seems to favor metastasis.

It has been suggested that injury favors metastasis because endothelial proliferation succeeding a trauma supplies a stroma in which a tumor cell may conveniently lodge and multiply.

The terms *primary* and *secondary* tumors refer to the original and the metastatic growths respectively.

Classification of Tumors.—No very satisfactory classification is possible at the present time, and it is unlikely that any will be constructed until more definite knowledge regarding the etiology is obtained. The older classifications were based upon the shape, the physical properties, or the nature (whether destructive or harmless) of various forms. Virchow offered a classification based on the histology of the new growths (histogenetic classification). According to this classification, fibroma, osteoma, chondroma, lymphoma, and sarcoma are included under the heading of connective-tissue tumors or tumors reproducing more or less accurately connective tissues. The different forms of tumors comprising the group are distinguished by their resemblance to one or another of the forms of connective tissue. Among the epithelial growths are papilloma, adenoma, and carcinoma, and in the same group should be placed glioma, which, though it superficially resembles connective-tissue tumors and arises from the neuroglia, a tissue resembling connective tissue in function, is really an epithelial growth, as the neuroglia is an ectodermal derivative. Among the tumors re-

producing muscle tissue are the two forms of myomata—the leiomyoma and rhabdomyoma.

This classification is eminently satisfactory in some cases, but fails in the case of mixed tumors containing a variety of tissues and in which the primary or essential constituent is not always obvious. Thus, in papillomata it is sometimes difficult to determine whether the growth was originally epithelial or originally of connective-tissue type.

Recently it has been suggested (Mallory) that a more careful study of the histological differentiation of the cells and intercellular substance may serve as a basis of classification of tumors. Three forms of fibrils, called *neuroglia*, *myoglia*, and *fibroglia fibrils*, have been distinguished, and have respectively been found in gliomata of various types, in leiomyomata, and in connective-tissue growths, including fibromata, fibrosarcomata, and spindle-celled sarcomata. The fibrils differ sufficiently to form the basis for the recognition of the character of the cells from which they originate, irrespective of the rate of growth or physical properties of the tumor.

Other pathologists have grouped tumors according to the embryological derivation of the tissues from which the new growths originate or of the tissue composing the tumor. It is perhaps wisest to attempt no classification of any kind, and in the following sections we have arranged the various tumors according to their histological characters, following in a general way the adult tissue types without attempting to establish groups.

CONNECTIVE-TISSUE TUMORS

FIBROMA

Definition.—A fibroma is a tumor composed of connective-tissue cells and fibers resembling those seen in fibrillar tissue.

It is derived from mesodermal cells which have the power to produce various kinds of fibrils. It varies from a slowly growing tumor composed of fibers almost exclusively up to rapidly growing new growths composed of cells, with little tendency to proceed to fiber formation. In the latter case it approaches a sarcomatous nature.

Etiology.—The causes of fibroma are as obscure as those of tumors in general. There are many facts, however, which point to the importance of irritation or injury as exciting causes. Among these may be mentioned the development of peculiar forms (keloids) in scar tissue and the resemblance of these tumors to spontaneous fibromata, and the appearance of fibrous nodules in the skin at points of friction or definite pressure or in places irritated by discharges.

It is impossible to draw sharp lines between fibromata and hyperplasias of connective tissue following irritation. In the skin and superficial tissues there occur hyperplastic connective-tissue processes, constituting elephantiasis, which in some cases are distinctly the result of irritation, and in other cases seem purely spontaneous. The elephantiasis of tropical countries, often due to occlusion of the lymphatic

channels by filariæ, and the thickening of the skin and adjacent connective tissue of the legs around old ulcerations or eczematous areas, are instances in which distinct irritation is the cause. On the other hand, congenital elephantoid conditions of the skin are seemingly spontaneous or causeless, and some of the cases in later life have the same characteristic. The diffuse hyperplasias of the viscera, though often distinctly inflammatory, may appear without adequate discoverable cause, and, according to the view of some authorities, are to be looked upon as diffuse fibrosis or fibromatosis, rather than as inflammatory conditions. In ordinary cases of sclerosis of the organs the connective-tissue growth is entirely diffuse, but thickenings may occur in certain situations, and the resemblance to tumor formation is then much more striking. This is sometimes the case in the liver, but particularly in the kidneys. In the breast there are cases in which no dividing line can be drawn between chronic interstitial mastitis and fibroma. The microscopical appearances are practically identical. A distinction, if

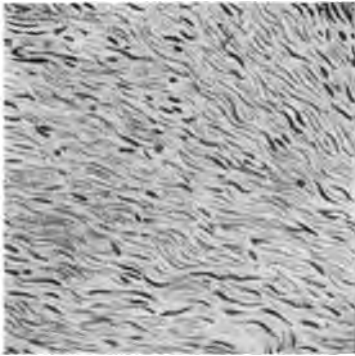


Fig. 49.—Hard fibroma (Warren).

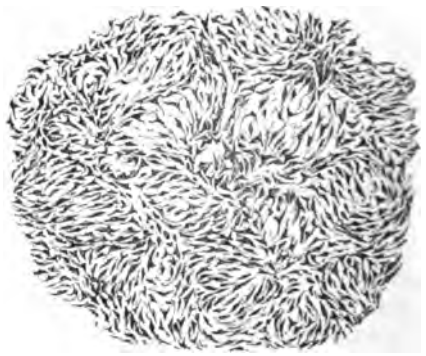


Fig. 50.—Soft fibroma of the subcutaneous tissue.

any can be made, is based upon the nodular character and spontaneous origin in the one and the opposite conditions in the other.

Appearance.—The naked-eye appearance of fibromata is usually quite characteristic. The tumor may be hard (Fig. 49) or soft (Fig. 50), according as it resembles dense or loose connective tissue in structure and according to the amount of edematous liquid or associated myxomatous degeneration of the intercellular substance. The growth is more or less rounded and usually enclosed in a distinct capsule. In the substance of organs it is spherical or tuberos, and when near the surface projects more or less. When it springs from a mucous or serous membrane or from the skin the weight of the tumor may gradually lead to a polypoid formation. Some of the fibromata of the skin are arborescent or dendritic in form, and keloids are frequently irregular or star-like in outline. The rounded and encapsulated tumors may be lobulated, though more frequently they occur in a uniform mass.

Seats.—The points of origin from which fibroid tumors arise are

very numerous, though they always spring from pre-existing connective tissue. Among some of the more common localities may be mentioned the subcutaneous connective tissue, the submucous tissue, the periosteum of bones, tendons and tendon-sheaths, and the fibrous covering of nerves. Of the internal organs, the uterus, the ovaries, the kidneys, and heart muscle are the most important. Less frequently fibromata are found in the serous membranes of the chest and abdomen or of the central nervous system. The fibroids of the skin, uterus, the nerves (see Neuroma), and the mucous membrane of the nose are the most important.

The mammary gland presents several interesting forms of inflammatory or fibromatous new growth. First, there is a diffuse form of interstitial mastitis in which the entire breast becomes indurated; this is distinctly inflammatory. In other cases nodular or lobular areas of thickening occur, and in these the evidences of inflammatory action are sometimes obscure or wholly wanting. Some of these are certainly



Fig. 51.—Intracanalicular fibroma (Perls).

instances of true fibroma (*fibroma mammae nodule*). In still another group of cases the fibromatous proliferation of the connective tissue projects into the tubules and acini of the gland, pushing the epithelium before it and sometimes sprouting or proliferating in polypoid form within the tubules. The gland in such cases may present a striking macroscopical appearance on section. Numerous cystic formations may be visible, with projecting dendritic formations within, causing an appearance somewhat like that of a section through a cauliflower (Fig. 51). Microscopically, the proliferations of the connective tissue between the tubules and projecting within the tubules constitute the characteristic features. The term *intracanalicular fibroma* has been given to such cases. Obstruction of the tubules in certain areas may lead to very marked cystic distention. Combinations with sarcoma are frequent.

Structure.—The definition explains the structure of fibromata. On section through the body of the tumor the fibrous nature may be revealed by a distinct concentric or radiating striation, particularly

in the case of hard fibromata. The softer varieties are much less likely to present this feature. The color is usually gray or whitish, and may be glistening when there is mucous degeneration, or yellow in the case of associated fatty tissue. Microscopically, a striking feature is the connective-tissue cell, which is rounded, star-like, and branching in the softer tumors, and compressed, spindle shaped, or elongated in the case of the hard varieties. Some authorities maintain that they are merely different stages of the same process. There are all gradations in this series. The intercellular substance is composed of a fibrillar network and homogeneous or granular material traversed by thin-walled blood-vessels, oftentimes having merely an endothelial coat. The parallel and wavy bundles of fibrils are the most conspicuous feature of hard fibromata. In softer varieties the fibrils are less often in bundles, and are twisted or irregularly curled. The fibrillar substance may be so closely packed that the intercellular substance has a glistening, hyaline appearance. This is very marked in keloids. Sometimes actual hyaline change affects the fibrils. Cavernous dilatation and rupture of the vessels may cause a distinct hemorrhagic appearance of the section, but such conditions are rare.

A true keloid is a fully formed connective tissue tumefaction without a capsule and tending to show hyalin degeneration. It is commonest in negroes. The epidermal layers and papillæ are correctly preserved. A false keloid arises in scar tissue. It is apt to show a limitation, but not by a distinct capsule, and the epidermis and papillæ are absent or distorted.

Secondary Changes in Fibroma.—In some cases embryonal round cells may be abundant and a distinct sarcomatous transformation of the tumor may occur. This, however, is rare. In other instances, as has already been remarked, myxomatous tissue may be conspicuous, and all grades of transformation, from a pure fibroma to a pure myxoma, may be met with, especially in the case of soft fibroma. Fatty degeneration of the cells and lipomatous infiltration or associated lipoma are also frequent. These forms, the myxomatous and lipomatous, are particularly frequent in the submucous and subcutaneous connective tissues. Calcareous change occurs in large fibromatous tumors, particularly in those of the uterus, and very rarely true ossification has been reported. Less commonly association of fibroma with other forms of tumor growth is found. Among these the combination of fibroma with leiomyoma is usual in the uterus.

Small fibromata about nerve-endings may be hard or soft. Some arise from the connective tissue of the nerve-sheath or from Schwann's membrane. A kind occurring on the skin in disseminated form is called molluscum fibrosum. There is also a painful variety upon or near nerve-endings. The nerve-fibers pass through or are caught by the fibroma and are not themselves changed.

Nature.—Fibroma is essentially a benign tumor, though recurrence occasionally takes place after removal, this being particularly the case with keloids and some of the polypoid growths of mucous membranes.

In some of these instances there is undoubtedly a resemblance to sarcoma, if not actual sarcomatous transformation. As a rule, fibroid tumors are destructive only in so far as they are capable of producing mechanical injury by pressure. The growth of the tumors is usually exceedingly slow. Metastases of pure fibroma do not occur, and the mass does not recur if removed completely.

MYXOMA

Definition.—Myxoma is a tumor composed of connective-tissue cells and an intercellular substance containing mucoid material in more or less abundance. The gelatinous substance of Wharton in the umbilical cord and the vitreous humor of the eye are normal tissue types which myxomata resemble in their structure.

Etiology.—The causes and the nature of myxomata are practically the same as those of fibromata, and intermediate forms make it difficult to draw a sharp line between the two. Less frequently myxomata are sarcomatous growths with myxomatous change.

Appearance.—A typical myxoma is a soft, more or less flabby growth, enclosed by a capsule and having a rounded outline. It may project from the surface of the body or of an organ as a hemispherical elevation, or may hang by a narrowed pedicle in the form of a distinct polyp. The latter is frequent in the mucous membranes, but may occur in the skin as well. Sometimes the tumor is lobulated, and the lobules may be visible or may be easily felt. Occasionally myxomatous growths are diffuse, having no capsule and marked by no definite limits.

Seats.—Among the common situations are the subcutaneous and submucous tissues and the connective tissues of certain organs, notably the mammary glands. They may occur along the course of nerves, and in the brain or the spinal cord. They sometimes spring from subserous tissues, notably from the interauricular septum and valves of the heart. The tumor may be solitary or, like fibroma, may be met with in numbers. Congenital myxoma has frequently been found.



Fig. 52.—Myxoma, showing stellate cells separated by a gelatinous (mucoid) intercellular material.

Structure.—Microscopically, the characteristic features are stellate or spindle-shaped connective-tissue cells which lie within a matrix of myxomatous material (Fig. 52). The latter is homogeneous or slightly granular, and somewhat refractive to light, giving the surface a glistening quality. The cells themselves may be entirely normal young connective-tissue cells, or they may present evidences of fatty degenera-

tion. Round, connective-tissue cells are met with in some instances, either scattered through the tumor or in certain areas, and may be so abundant as to justify the term "myxosarcoma." The vascular supply is usually poor, and the blood-vessels resemble those of fibroma in being only partially developed. Association with fibroma and lipoma is frequent. Cartilaginous tissue may be found in myxomatous tumors of the parotid gland or testicle, and in these cases the myxomatous portion is rather an association than a degeneration of an original chondroma. Myxomatous degeneration of chondromata, osteomata, fibromata, and sarcomata is, however, a frequent occurrence.

Nature.—Myxoma is benign like fibroma, but recurrence is not infrequently observed, and in a few instances metastasis has been reported. In these cases the growth was doubtless sarcomatous, with associated mucoid tissue. When myxoma becomes sarcomatous the cellular content increases and the mucoid material is absorbed. The growth of myxomata is slow.

LIPOMA

Definition.—A lipoma is a tumor composed of fatty tissue like that of the normal subcutaneous tissue. The epiploic appendages of the intestines are the normal type which lipomata resemble. They are derived from the fat cells and not from fibroblasts. The fat is the same as natural subcutaneous adipose tissue in chemistry, except that the lecithin is somewhat less in amount.

Etiology.—There seems to be a tendency, consisting perhaps in some derangement of the trophic nervous system, to the growth of these tumors. It is difficult at times to draw a sharp line between circumscribed lipomata and diffuse fatty growth. Localized fatty or myxolipomatous accumulations in myxedema and a curious and apparently causeless deposit of fatty tissue sometimes observed in the subcutaneous tissue of the neck in men, represent the border-line between lipomata and ordinary obesity. Some individuals have a marked liability to constant overgrowth of fat in different parts of the body, and the term "lipomatosis" is not inapplicable. This fatty growth does not apparently depend upon the character or quantity of food, nor even upon sedentary life in some cases, but rather on an obscure tendency to adipose accumulation. The importance of the hypophysis and gonads to such conditions has been the subject of much fruitful investigation in recent years.

Traumatism seems to play no part in the etiology of lipoma, though fatty infiltrations are prone to occur around areas of injury or disease and in degenerated organs.

Appearance.—Lipomata are usually circumscribed and encapsulated tumors having a lobulated character, the latter being due to septa of connective tissue. On the surface of the body they appear as somewhat hemispherical elevations which may reach enormous proportions. Rarely they become polypoid. In the interior of the body, as, for example, when they arise in the submucous or subserous connective

tissue, they are very frequently, though not always, polypoid. Sometimes they become detached and may be retained in one of the cavities of the body as free bodies. On section, the appearance is that of fatty tissue, though in some cases it is more firm from the association of fibrous tissue, and in other cases less firm from the nature of the fatty tissue itself or from associated myxomatous change. Lipomata may be solitary tumors or there may be many. As a rule, they appear in adult years or middle life, but congenital lipomata are not very rare; occasionally they are found to begin in childhood.

Seats.—Among the situations in which lipomata occur the most common are the subcutaneous fatty tissue of the back, shoulders, buttocks or limbs, the submucous and the subserous tissues. They may arise either in the normal fatty tissue or in connective tissues in which fat is not normally present. Some authors, however, deny the possibility of lipomata arising excepting from pre-existing fatty tissue. Of the organs, the mammary gland and the kidney are most frequently involved.

Structure.—Microscopically, lipomatous tumors resemble the normal fat. It is notable that the cells are larger—that is, contain more oil—than the normal fat cells, and this is strikingly the case in some instances, but is not always demonstrable. The vascular supply is about the same as in normal fat, though occasionally large vessels with thin walls are seen. Associated myxomatous or fibrous change may cause a variation of the microscopical appearance. Lipomata may undergo softening from necrosis, but more frequently become calcareous in part or completely.

Nature.—This is the most benign form of tumors. Recurrence after more or less complete removal does, however, at times occur. A lipoma is dangerous only from its weight or position. It does not contribute to the support of the system in case of starvation.

XANTHOMA

Definition.—This term is applied to two possibly distinct though similar forms of new growth. The *xanthoma vulgare* occurs most frequently in the eyelids and may be confined to that situation. The growth appears in the form of flat elevations of a yellow color. Generalized xanthoma beginning about the eyes is less frequent. *Xanthoma diabeticorum* is a similar affection of diabetic patients. It occurs at a more advanced age, is more distinctly inflammatory, the masses are more rounded, and the eyelids and face are rarely affected. Xanthoma is frequently associated with hepatic disease.

Structure.—The histology of xanthoma is that of modified fatty tissue. It resembles embryonal adipose tissue, and there is usually more or less round-cell infiltration as well. Some authors regard the latter as a tendency to sarcomatous change; others look upon it as inflammatory. It lies chiefly in the corium, but the subcutaneous tissue may be involved. Cholesterol combinations have been found in these tumors.

Nature.—Xanthoma is eminently benign. The diabetic form is subject to sudden and apparently causeless involution. The ordinary form may similarly subside, though much less commonly.

CHONDROMA

Definition.—A chondroma is a tumor composed largely or entirely of cartilage. The parent cell is, of course, the chondroblast in the perichondrium, a fibroblastic cell which has, in addition, the power to lay down a ground substance of chondromucin. When this predominates in tumors they have a hyaline appearance, but when the fibers predominate the resulting mass follows the white fibrous or yellow elastic cartilage types. It is difficult to draw a sharp line between outgrowths of cartilage from existing cartilage or bone due to irritation from definite and independent tumor-like growths. A group of cases of intermediary character is that including cartilaginous nodules formed in tendons of muscles subjected to frequent irritations, as in the deltoid muscles in soldiers carrying heavy arms, and in the adductor muscles in the thigh in horseback riders. In these cases normal connective tissue seems to be directly transformed into cartilage, though the influence of irritation is undoubted.

Etiology.—A congenital disposition, sometimes hereditary, is unquestionably present in certain cases. Virchow maintained that chondromata often spring from remnants or islands of cartilage left in abnormal situations, as in the midst of bone, as the result of imperfect fetal development. The same explanation would account for parotid chondromata on the assumption that parts of the branchial arches are misplaced and remain in the substance of the parotid gland. Other evidences of the truth of the theory are the frequent occurrence of chondromata at the epiphyseal ends of bones, and the appearance of such growths in early life and especially in rachitic individuals.

Irritation has been referred to. Direct traumatism is sometimes the cause of cartilaginous outgrowths from bone, particularly when fractures have occurred.

Appearance.—Two distinct forms may be considered, and these are somewhat different in appearance. They are: (1) cartilaginous outgrowths, *ecchondroses* or *ecchondromata*, and (2) cartilaginous tumors or *chondromata* proper, originating in non-cartilaginous tissues.

Ecchondromata present themselves as encapsulated, rounded, or somewhat irregular outgrowths from cartilages. Sometimes they are wart-like in form, and may occur in rows or groups. They may be firmly attached, or may be loosely united to the cartilage from which they spring. The most frequent (though not strictly neoplastic) are the outgrowths in the articular cartilage occurring in chronic arthritis, particularly in arthritis deformans. Occasionally they become detached after their formation, and in the joints may thus become free bodies. More characteristically tumor-like *ecchondromata* originate from the surfaces of the laryngeal cartilages or from the costal cartilages.

Chondromata proper most frequently occur in bones or the periosteum, and have a rounded or lobular appearance.

Chondromata springing from the inner surface of bones (possibly originating from the marrow itself) may grow uniformly by repeated or constant proliferation and occasion globular swellings of the affected bones (Fig. 53). The true bony covering becomes more and more thin until it may actually be perforated.

The true chondromata are usually rounded bodies of dense elastic consistency and the pale blue color of cartilage; they present lobular irregularity when they reach considerable size, the lobules being separated by connective tissue.

Chondromata are usually hard, though secondary softening may occur. In cases in which association of mucous, sarcomatous, or other soft tissue is present the consistency is correspondingly less. In some cases central softening leads to cystic formation. The liquid in the cyst is more or less turbid and occasionally sanguinolent.

Seats.—Ecchondroses and chondromata, for the most part, take their origin from bone, cartilage, or periosteum. The ecchondromata originate from the perichondrium rather than from the cartilage itself. In some cases chondromata originate in connective tissue, as that of the tendons, by a process of cartilaginous metaplasia. Cartilage tumors are met with in some of the glandular organs, notably the parotid gland, testicle, and ovary; and rarely they occur in the lungs, especially at the root and springing from the peribronchial cartilages.

Ecchondroses are most frequent about the long bones, as those of the extremities, and particularly at the epiphyseal attachments, where they may reach considerable proportions. Situations of great clinical importance are the interpubic and occipitospheoidal junctions. In the former situation ecchondroses projecting inward may interfere seriously with labor, and in the latter place cartilaginous outgrowths may penetrate the dura and exercise injurious compression on the brain. Allusion has been made to the ecchondroses of the joints in arthritis.

Chondromata proper may occur in the neighborhood of bones, in the muscles and tendons near their bony attachments, and in the organs mentioned, but in the last situation are rarely pure, myxoma being the most frequent associate.

Structure.—Chondromata resemble hyaline, fibrous, or elastic cartilage, the first named being much the most frequent. The tissue



Fig. 53.—Chondroma of the thumb (Warren).

differs from normal cartilage in the fact that the cells are frequently without capsules and are much less regularly arranged (Fig. 54). The intercellular substance is more abundant, and is frequently gelatinous, mucoid, or fibrous, and not rarely the different types of cartilage occur within narrow limits. Association with myxoma and sarcoma, or both, is common, especially in the parotid and testicles, the proportion of the several ingredients varying greatly. Tumors of this kind are spoken of as *mixed tumors*. Calcification and true ossification are not infrequent, particularly in cartilage tumors intimately connected with bone. The term *osteochondroma* is applied in such cases. The name *osteoid chondroma* is applied to chondromata in which the intercellular substance is trabecular in arrangement, suggesting bone structure, but in which actual ossification has not occurred. Such growths are met with about the bones and, as a rule, spring from the periosteum. The cartilaginous part of these tumors is without blood-vessels.

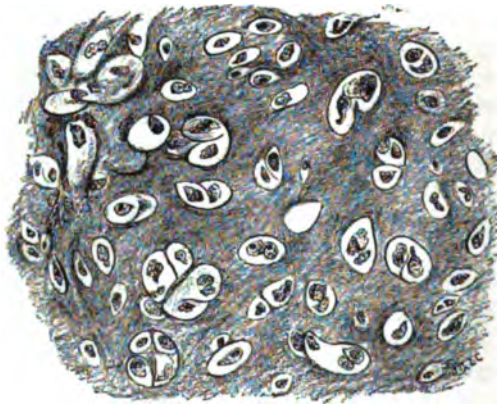


Fig. 54.—Chondroma of the hyaline type.

Degenerative changes are frequent because while the tumor as a whole is vascular the islands of cartilage are not, and the parts removed from the vessels get little nutrition. Myxomatous degeneration may occur, though myxoma is more frequent as an association than as a degeneration. Softening may occur in the center of the mass, and may lead to cyst formation, this being particularly common in the myxochondromata. Growths of this kind are frequently quite vascular and hemorrhages into the cysts may occur. Eventually such cases may show scarcely any cartilage cells, a few being perhaps detected in some part of the cyst wall. A single hard lump may be left at one side of the cyst, the rest of the tumor having softened.

The more cellular the tumor, the greater the tendency to sarcomatous degeneration. Fibrillation and cell increase are early indications of such a change.

Nature.—Chondromata are usually benign, and are dangerous only through the pressure they exert. Removal of a part of the tumor may

have a beneficial influence in causing calcification of the remainder. Metastasis may undoubtedly occur in pure chondromata through transportation of particles in the circulation; such cartilaginous emboli have often been demonstrated. The secondary growths are most frequent in the lungs. Metastatic chondromata are, however, more frequently chondrosarcomata than pure chondromata.

OSTEOMA

Definition.—An osteoma is a tumor composed of osseous tissue. Osteomata are closely allied to cartilaginous tumors, and frequently transformations occur. The cell of origin is the osteoblast, as adult bone cells do not reproduce.

Etiology.—The same difficulty is experienced in distinguishing inflammatory outgrowths or exostoses from true bony tumors, as in the case of cartilaginous growths. Enlargement of the facial bones in leontiasis ossea, of the bones of the extremities in acromegaly and

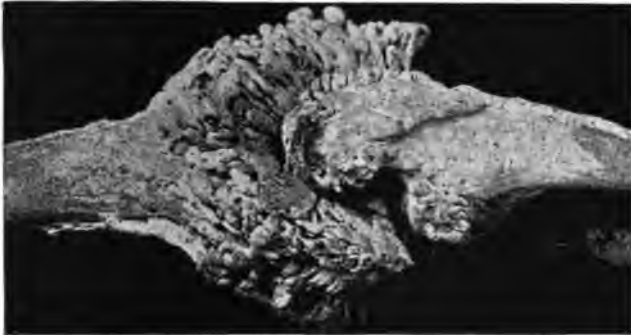


Fig. 55.—Exostoses of the elbow-joint.

hypertrophic pulmonary osteo-arthritis, and ossification of the muscles in myositis ossificans, are instances of border-line conditions separating true tumors from inflammatory hyperostoses. Irritation and traumatism undoubtedly play a part in the etiology, even in neoplasms unattached to the bone, and in the case of bony outgrowths injury is generally the immediate cause. An underlying predisposition undoubtedly exists, and explains the occurrence of congenital multiple bony tumors.

Appearance.—Two forms may be distinguished, as in the case of chondromata: (1) outgrowths or exostoses and osteophytes, and (2) the osteomata proper, or heteroplasmic osteomata. Exostoses and osteophytes are distinguished one from the other by their shape and appearance rather than by any essential difference. The former are direct outgrowths of more or less wart-like character; the latter are more extensive and present the appearance of bony deposits upon bones, and are less closely attached (Fig. 55). In both forms the surface of the growth is irregular, nodulated, or wart-like (Fig. 56). The consistency

is that of bone, and the size varies from that of small outgrowths to masses as large as a fist. On section, two forms may be distinguished: the hard or *osteoma durum*, after the nature of compact bone with fairly well imitated architecture; and the soft or *osteoma spongiosum*, after the character of spongy bone, but less well arranged, more of the embryonic cell type and more apt to show degenerative changes. Sometimes the substance of the tumor is exceedingly dense, and the term

osteoma eburneum is applied. This form is without the completed Haversian systems, and osteoblasts are apt to be wanting over large areas.

There may be osteomata of endosteal origin arising from endosteum or misplaced cartilage.

The heteroplastic osteomata, or those separated from the bone, are more rounded and, when of considerable size, usually nodulated and lobulated. In the serous membranes they occur as flat bony plates.

Seats.—Osteomata spring from the bone or cartilage, or from connective tissue near the bones. More rarely they

Fig. 56.—Osteoma of the lower jaw (Warren).

arise in other connective tissues, in the serous membranes, or in certain organs, notably the testicle and parotid gland.

Osteomata connected with bones are most frequent about the epiphyses, at the attachments of muscles, or at the seat of old fractures from which abundant callus has been deposited. The skull bones may be affected on the outer or inner surface, and often an elevation is noted without and within at the same spot. A form of clinical importance is that in which exostoses occur on the inner aspect of the metatarsal bone of the great toe from compression of tight shoes. In the maxillary bones osteomata may originate about the roots of malformed teeth. In cases of accumulation of cement substance beginning at the neck of the tooth the term *dental osteoma* is applied; these are strictly comparable to osteomata. In cases in which proliferation of the dental pulp has occurred the term *odontoma* is applicable, and the tumor is not of osseous character. The bony growths sometimes seen in the serous surfaces nearly always arise in areas in which there has been thickening from chronic inflammation. They are most frequent in the dura mater of the brain, particularly the falx cerebri, though the membranes of the cord, the pleura, endocardium, or pericardium may be involved.

Structure.—Microscopically, osteomata resemble more or less accurately bone tissue. They vary, however, in different areas, and mixtures of cartilage with bony tissue are frequent. Secondary degenerative changes (softening) may occur, and association with tumors of other character are not infrequent (chondroma, myxoma, fibroma, sarcoma).

Nature.—These growths are eminently benign, slow of growth, do not recur, and do not give metastasis. Their situation sometimes makes them troublesome or dangerous.

ANGIOMATA

This name is given to tumors the chief part of which is made up of vessels with a relatively small amount of supporting tissue. It is by growth of new vessels or increase of tortuosity of those existing that these tumors grow. The interstitial tissue may undergo change, but the principal feature is vessel sprouting.¹

LYMPHANGIOMA

A lymphangioma is a tumor composed of dilated lymph-vessels or lymph-spaces, more frequently the latter. It is difficult to separate dilatations of lymphatic channels due to obstruction from hyperplastic processes. Congenital enlargements of certain parts are met with which seem entirely dependent upon the abnormal development of the lymph-spaces. These constitute the condition called *elephantiasis congenita mollis*, in which the subcutaneous tissues are boggy or edematous, and even distinct cystic formations occur. *Congenital cystic hygroma* is an instance of dilatation of the lymph-spaces. Congenital enlargement of the tongue, termed *macroglossia*; of the lips, *macrocheilia*; and of the skin, *nævus lymphaticus*, are other instances of the same process. In all of these, in addition to the dilatation of the lymphatic spaces, a marked proliferation of the connective tissues as well as the muscle (in the case of the tongue) is striking; but the process, in all probability, originates as a dilatation of the lymph-spaces. The term *lymphangioma cavernosum* has been suggested for these cases of dilatation of the lymph-spaces. On staining with silver-salts the endothelial lining of the spaces may be readily demonstrated. Actual enlargement and varicosity of existing lymphatic vessels may occur, but is extremely rare in the form of circumscribed growths; it is met with more frequently in association with general processes, such as elephantiasis. The bursting of dilated lymphatics may lead to *lymphorrhæa* or external discharge of lymph when the process involves the skin, or to effusions of lymphatic character when the serous cavities are involved. Chylous pericarditis, pleuritis, and ascites are thus produced. Rupture of dilated lymphatics along the urinary tract (kidney or bladder) occasions *chyluria*. Lymphangioma is a benign process in the pathological sense. This classification is here limited to those tumors in which vessel change is the only feature, growths arising from lining or covering membranes being placed among the endotheliomata.

¹It is maintained by some that these are not true tumors, as they have no power of independent growth and keep pace with the body growth by reason of obstruction or an error of tissue resistance. The term "hamartoma" has been applied to them.

HEMANGIOMA

Definition.—A hemangioma, or angioma, as it is more frequently called, is a tumor-like formation composed principally of blood-vessels. Two varieties may be described, that which simulates merely distended capillaries and veins (*angioma telangiectaticum*), and that in which there are enlarged spaces lined with endothelium (*angioma cavernosum* or *cavernoma*). In many tumors the blood-vessels are somewhat enlarged; these are spoken of as telangiectatic tumors.

Etiology.—Congenital malformation certainly plays some part in some cases, as the frequency of hemangiomata in the newborn and particularly at the junction of the branchial arches would indicate. Injury, however, and mechanical causes generally also play a part, and pre-existing disease, particularly fibroid inflammatory processes, may contribute to the subsequent dilatation and proliferation of the vessels (see below).

Appearance and Seats.—The angioma telangiectaticum may consist merely of delicate capillaries and arterioles, and in this case a bright red color is observed. The tumor appears as a spot on the surface of the skin, more or less sharply outlined from the surrounding tissue. It is not elevated and has the same consistency as the healthy parts. Usually it occurs as a multiple condition, and the larger are often surrounded by smaller spots. The skin is the favorite seat; but the subcutaneous adipose tissue and sometimes the mucous membranes are involved. Less commonly larger (venous) channels occur in the tumor, when a dark red color is observed (port-wine stains).

If a circumscribed portion of the circulation is uniformly involved, the vessels thicken and elongate, and a peculiar form of hemangioma results. In these cases the arteries are greatly thickened and tortuous, and form bunches under the skin, suggesting to palpation a bundle of earth-worms; while the surface of the skin presents peculiar irregular elevations without, of necessity, any change of color (*aneurysma racemosum seu cirsoideum*). This is not infrequent in the scalp. A similar condition of the vessels is observed in the varicosity of the legs, labia, or other parts. It is most frequent in the hemorrhoidal veins, constituting the ordinary hemorrhoids. (These conditions do not strictly constitute tumors and will be more fully described in discussing the diseases of the vessels.)

Cavernous angiomata present themselves as more distinctly tumor-like formations of dark venous color, involving the skin or subcutaneous tissues, the retrobulbar tissue of the eye, the mucous membranes of the nose or pharynx, and certain organs, as the mammæ, the kidney, the spleen, but particularly the liver. Like the other variety, they may be congenital, but more frequently arise in later life, especially that of the liver, which is most common in old persons. The appearance is that of a more circumscribed tumor, sometimes showing a distinct capsule and varying in consistency with the degree of distention of the blood-spaces. In the skin it projects slightly from the surface (*nævus prominens*).

Structure.—The definition explains the structure in general. The blood-vessels of telangiectatic angiomas may be simply dilated capillaries with a lining of endothelium and a fibrous outer coating. More commonly the vessels are considerably thickened and held together by a reticular connective tissue. In rare instances the vessels are so closely packed and the walls so thickened that when the blood is removed the appearance is not unlike that of the tubules of a sweat-gland. The congeries of vessels of a telangiectatic angioma represents the elongated and tortuous vessels of the affected area, and also new-formed vessels originating from the former. The only connection of the angioma with the general circulation is through one or a few afferent arterioles and efferent veins. The growth is not merely an enlargement of pre-existing vessels, but an actual new formation.

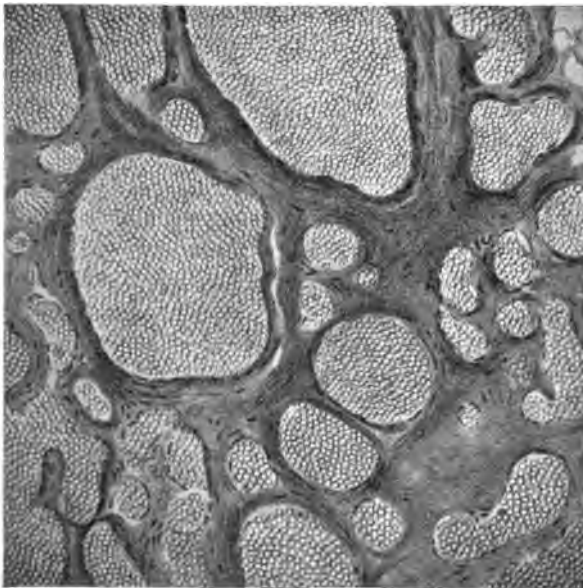


Fig. 57.—Cavernous angioma (Warren).

The cavernous angiomas present large spaces lined with endothelial cells (Fig. 57). Between these spaces are parallel fibers of connective tissue which form the framework of the tumor. In cases involving the liver the proper substance of this organ disappears completely, leaving only anastomosing spaces with a fibrous framework. Virchow taught that the fibrous process was primary, and by traction and pressure gradually induced dilatation of the vessels and atrophy of the liver substance. Some of the more recent writers believe that the dilatation of the vessels is the primary condition. The capsule sometimes found surrounding the cavernous angioma is certainly a secondary formation.

Angiomas of the skin may enclose the hair-follicles and sweat-glands; those of the subcutaneous tissue frequently show areas rich in

fatty tissue (angiolipoma); secondary angiomatous change of tumors is probably the result of dilatation of the pre-existing or new-formed vessels. Sometimes secondary change may occur in the connective tissue of the vessels of an angioma, as in the plexiform angiosarcomata, in which the blood-vessels are surrounded by ensheathing sarcoma-cells (see Fig. 57). Certain cylindromata have the same origin.

Nature.—Angioma is essentially benign, and may continue through life without enlarging. Hemorrhage and inflammatory or necrotic changes are its dangerous consequences.

LYMPHADENOMA

Definition.—This term is here used to designate a more or less malignant form of new growth affecting the lymphatic glands or other lymphadenoid tissues, and having the structure of lymphatic tissue. From a clinical and anatomical standpoint the manifestations of this condition are manifold, but histologically they have the same origin. They all arise from the lymphoblast, the endothelia, or both. Thus in the varieties lymphosarcoma and Hodgkin's disease the younger cells, or those nearer the parent cell, predominate, while in lymphoma and lymphatic leukemia the last stages of the lymphocyte series are more numerous. We shall consider under this heading the hyperplasias of lymph-tissue giving rise to tumors, leaving for the chapter on the Blood the leukemias, whose histogenesis is the same. (For discussion of Tumors of Lymph-glands, see p. 461.)

There are several grades of lymphomatous disease, starting with simple lymphoma of nearly typical lymph-tissue structure and ending with true sarcoma of lymph-nodes, which, of course, are of the small round-cell type. To differentiate between closely related conditions is a problem of great difficulty and questionable utility. There are discussed here simple lymphoma, lymphomatosis, and Hodgkin's disease, conditions affecting the lymphocyte-producing organs, yet, curiously enough, failing to produce any marked alteration of lymphocyte content in the blood. With the exception of simple lymphoma, a rare, probably hyperplastic or inflammatory condition, these diseases seem to be systemic, since change in one locality is followed by lymphoid overgrowth almost universally in the body.

Etiology.—There are cases of infectious enlargement of the glands and traumatic swellings that cannot be clearly distinguished from lymphadenoma. In some cases even the clinical course is the same and a separation seems impossible. For example, the glands in a number of instances of Hodgkin's disease (as far as the clinician can establish this diagnosis) have been found to contain tubercle bacilli. We must conclude that general lymphatic tuberculosis may occur in clinical forms indistinguishable from Hodgkin's disease, but cannot assert that this establishes the pathological identity. Tubercle bacilli have been discovered in some cases diagnosed as lymphomatosis (Sternberg and Gross), and in other cases where they were absent, Fränkel and Much

have found Gram-positive rods or coccus-like bodies which Much claims to have shown are tubercle bacilli having lost acid-fast properties. The large number of eosinophiles in the gland speaks rather against the tuberculous nature of the growth. The presence of tubercle bacilli may, furthermore, be explained as sometimes the result of secondary infection. In a number of well-studied cases the absence of tubercle bacilli has been proved by the inoculation of animals.

Various micrococci and bacilli have been discovered in glands from cases of Hodgkin's disease. This condition has lately been ascribed to a pseudodiphtheria bacillus which can be isolated from the glands by a special technic. Some have claimed to have reproduced the disease in monkeys by injection of the bacteria, but this must be corroborated. Others claim good results in treatment of clinical cases by the use of bacterins of this newly discovered organism. It is important, however, to note that similar diphtheroid organisms have been isolated from other diseases of lymphatic glands. In a few instances bodies resembling protozoa have been discovered.

Appearance and Seats.—Lymphadenomata present themselves as enlargements of the lymphatic glands of a single group or, more commonly, of a number of groups in different parts of the body. All of the glands of the group may be involved, or only a few. The individual glands retain their shape, as there is usually no tendency to extension beyond the capsule of the gland. In exceptional cases, however, the process is of a more infiltrating kind and the capsule is penetrated or destroyed. These instances merit the special term "lymphosarcoma."

Lymphadenomata may be *soft* or *hard*, according to the amount of connective tissue and the denseness of the cellular infiltration and proliferation. On section, the tumors are found to be grayish or whitish in appearance, and exceptionally may show slight areas of necrosis or softening. Extensive softening is exceedingly rare. The individual glands of the group may be clearly distinct, or may be fused together by interglandular connective-tissue overgrowth or by the penetration of the lymphadenomatous process through the capsule.

When superficial lymphatic groups are involved, tumors of various sizes are produced, and project as knobby or rounded enlargements beneath the skin. The latter is freely movable over the tumor unless the growth has penetrated the capsule or secondary inflammatory changes have occurred. In the case of internal glands large intrathoracic or abdominal growths may be formed, and may exercise destructive compression of vital parts.

Similar lymphadenomatous growths may spring from the lymphatic tissues of the gastro-intestinal tract—tonsils, lymphatic follicles of gastric and intestinal mucosa.

Sometimes the primary growth seems to begin in the thymus gland or its remnant (Fig. 58). Tumors of considerable size are produced in these cases, and their origin is recognized by their shape (two lateral parts united by a sort of isthmus) and by the absence of the appearance of a conglomeration of glands. In these cases the adjacent glands

and, later, more distant groups are involved. Lymphadenoma may be confined to the glands, but frequently extends to the solid organs by metastasis. The spleen, liver, and kidneys are the organs most frequently affected. They become enlarged and indurated, and on section show light colored areas of lymphadenoid tissue. Similar "lymphoid infiltration" may be seen in the heart, lungs, or other parts.

Lymphadenoma may affect the bone-marrow secondarily and perhaps primarily. (Reference will be made to this under the title Myeloma.) Sometimes the tumors have a yellow or green color and are called *chloromata* (q. v.).



Fig. 58.—Lymphadenoma (lymphosarcoma) probably originating in remnant of thymus gland: the tumor covered the upper part of the heart like a hood. The illustration shows the tumor turned upward and exposing the pericardium on its under surface.

Structure.—Histologically, the glands in the earlier stages show a hyperplasia of lymphadenoid tissue with predominance of small cells (lymphocytes). Later larger cells with pale nuclei make their appearance. Most of these are bizarre forms of the proliferating lymph-cells, while some are swollen endothelium from the sinuses. They may enlarge to form mononuclear or polynuclear giant-cells, the nuclei dividing by amitosis. Sometimes large areas of nucleated protoplasm (syncytial tissue) are observed. At this time the gland section is generally homogeneous in arrangement, all parts actively growing, and the architecture of follicles, cords, and sinuses is largely obliterated. Coincidentally with the appearance of these epithelioid and giant-cells there is formed a reticular fibrous network which increases with the age of the process until the gland becomes quite indurated. A somewhat char-

acteristic, though not constant, feature of the histology is the presence of numerous eosinophile leukocytes scattered through the tissue or in small masses. These may be mononuclear or polymorphonuclear. Plasma-cells and mast-cells may be present, but are not characteristic.

In the rapidly growing form, commonly called "lymphosarcoma," the cells, while still near the parent type, are more uniform in size and shape, more deeply staining, more active in proliferation, and there are fewer endothelioid and eosinophilic cells than in the Hodgkin's type. The clinical history may be the same, and one cannot now state the reasons for these differences, unless they be stages of the same process, a view held by some observers.

The above description leads one from the hyperplastic lymph-gland to the fully developed adenoma, made up of imperfectly differentiated cells. It is well to emphasize that in Hodgkin's disease the picture is dominated by large endothelioid cells in group arrangement mixed with groups of small lymphoid cells; many eosinophiles are to be found. There is a fine fibrosis running through the tissue. Focal necroses are common.

The spleen may show similar changes, beginning in the Malpighian bodies, but in many cases is affected in but slight degree or not at all.

The bone-marrow presents a picture of proliferation of myelocytes.

The liver, kidneys, lungs, gastro-intestinal mucosa, and other tissues may be extensively involved, presenting new formations of the lymphoid cells similar to those in the glands and originating from the lymphoid masses normal to these parts. These lesions were formerly regarded by most authorities as simple metastases, but are now thought by many to be proliferations of existing lymphoid tissue. Some, as Ribbert, hold that they are metastatic and are due to proliferation of metastatic cells, which, however, are attracted to pre-existing lymphoid collections by a species of chemotaxis that seems to invite the deposit of cells in areas where similar cells exist.

The occasional perforation by the growths of small blood-vessels with proliferation within the vessels is an argument in favor of the neoplastic nature of the process.

Nature.—Lymphadenoma is variably malignant. In a small proportion of the cases this malignancy is of local character—that is, the growth tends to invade the neighboring parts. In most instances there is rather a tendency to general involvement of the lymphatic system, with secondary growths in various organs. To cases of this kind the terms "Hodgkin's disease," "pseudoleukemia," and "adenia" have been given. These cases present themselves in the form of a progressive anemia (lymphatic anemia—Wilks), often with irregularly relapsing fever (chronic relapsing fever—Epstein), and especially with lymphadenomatous tumors in the superficial or deep lymphatic groups (axillary, cervical, inguinal, mediastinal, or abdominal). The disease progresses more or less rapidly, and terminates in death from cachexia and exhaustion in from one to three years. Occasionally the course is rapid, repeated hemorrhages or purpura may occur, and a fatal termination

is reached in a few weeks or months. The whole course of the disease is in these cases suggestive of an infectious process. The chronic cases may be infectious or due to some form of toxemia, but are at present more appropriately considered under the head of Tumors.

The relation of Hodgkin's disease and leukemia, especially the lymphatic type, is certainly very close. The glandular tumors and the secondary changes in the organs are somewhat similar, excepting that the lymphatic glands are more prominently involved in ordinary lymphadenoma and the marrow changes more striking in leukemia. The striking difference is found in the blood. In leukemia there is marked and characteristic leukocytosis; in the other condition this is absent. Many cases have, however, been observed in which Hodgkin's disease has apparently become leukemia; and some authors do not hesitate to speak of the two diseases as identical and representing merely two stages of a common affection. According to this view, we might classify different cases as either *leukemic* or *aleukemic lymphadenomata*. The blood in aleukemic cases shows more or less pronounced reduction in the number of red cells, and a normal, reduced, occasionally a moderately increased, number of leukocytes. The small mononuclear leukocytes are sometimes in relative excess. In acute cases nucleated red cells may be found.

The causes and nature of the irregular fever are uncertain. It may be due to an infectious cause, or may be the result of breaking up of leukocytes and liberation of ferments.

Multiple Myeloma.—This growth affects the sternum, ribs, vertebræ, skull, and, less frequently, other bones. The tumor at first suggests a hyperplastic condition of the marrow; later the substance of the bone is replaced by the growth, which may finally break through the shell of bone covering it and invade the soft tissues. Metastasis is very rare. The growth has a mottled grayish and reddish appearance and is rather soft. Microscopically it is composed of small round cells and a vascular network of thin-walled vessels. The cells resemble small myelocytes or, possibly in some cases, plasma-cells. There is also a type, the lymphoid, in which lymph-cells predominate. Bence-Jones albumose is found in the urine in cases of myeloma.

Chloroma is the name given to the greenish solid hyperplasias of the bone-marrow growing from the premyelocytes and owing their color to an abundance of lipochromes. This color vanishes on exposure to air. The tumor is probably merely a condensation of hyperplastic marrow in cases of myelogenous leukemia, as certain differentiations of the component cells into granular myelocytes, the occurrence of typical leukemic metastases, and the development of an enzyme acting in alkaline medium, all point in the direction of a hyperplasia of leukocytic elements. The superficial resemblance of the premyelocytes and large lymphatic cells has led to the erroneous opinion that chloroma was a lymphosarcoma, so that the names "myeloid" and "lymphoid" have been given to those cases in which respectively the granular and non-granular myelocytes have predominated. The similarity of the latter

and large lymphatic cells is marked, but all the cells of chloroma are now thought to be derived from the myelocytic series.

SARCOMA

Definition.—The term “sarcoma” is applied to tumors composed of connective-tissue cells with very little intercellular substance. It is often said that sarcoma-cells resemble those of embryonal connective tissue; properly speaking, they may be likened to the ordinary connective-tissue cell falling short of complete development—that is, no formation of fibrous intercellular substance, but a great tendency to continuous cell proliferation.

Etiology.—Of all the tumors, sarcoma furnishes the best ground for Cohnheim's theory. Its frequent occurrence in young persons, the relation of melanোসarcomata to congenital pigment-spots of the skin, and the sarcomatous mixed tumors of the parotid and testis were cited by Cohnheim among the evidences pointing to a congenital origin. Traumatism and inflammation certainly play some part, either in stimulating sudden growth of a latent sarcoma or in developing a lesion from which sarcoma springs. The parasitic theory has gained many adherents in recent years, though no specific organism has been demonstrated. Experiments at implantation of the disease in animals have been partially successful, but do not establish an infectious character, as has been shown in preceding pages. It is not improbable that certain lympho-sarcomata may be due to the action of bacteria.

Appearances.—Sarcomata are generally more or less rounded tumors, often enclosed by a limiting reactive inflammation of the neighboring tissues; they may, however, be irregular, infiltrating, and, therefore, unencapsulated. The growth of sarcomata is from the tumor cells themselves. The tumor spreads into the surrounding tissue and absorbs it, probably only retaining such connective tissue as it requires. A true fibrous capsule, made by the tumor and within which it grows, does not occur in sarcomata. Some forms appear on surfaces, spreading as flat elevations more or less irregular in outline. The consistency is soft or hard according to the number of cells and the amount of intercellular substance, or according to the kind and amount of associated tissue (myxomatous, chondromatous). Typical sarcoma, as the name implies (*σάρξ*, flesh), is flesh-like in consistency, and frequently, on section, the color is pink or of a flesh-tint. Many of the sarcomata, however, are quite white or gray, and a whitish liquid exudes from the surface on section.

Dilatation of the blood-vessels may cause a decidedly hemorrhagic appearance, and actual hemorrhages may take place, causing blood-cysts or, subsequently, serous cysts. Other degenerative changes, such as necrosis, mucoid change, and simple liquefaction necrosis, may render sarcomata soft and often cystic. Sarcomata of glandular organs like the breast may present a cystic appearance in consequence of compression, and subsequent dilatation of the glandular ducts and acini.

Angiosarcomata (the variety in which sarcoma-cells spring from the adventitia of blood-vessels) present themselves as more or less irregular growths, frequently flattened and branching when the surfaces of organs are involved.

Secondary sarcomata are nodular in character and nearly always present a capsule if the size is at all considerable (Fig. 59). They are usually white or pinkish; rather firm on section, but with a tendency to central necrosis or softening. In some cases almost every part of the

body may be studded with minute white spots scarcely distinguishable from miliary tubercles. This condition is called *sarcomatosis*.

Seats.—Sarcomata spring from pre-existing connective tissues, such as the subcutaneous, intermuscular, periosteal, or tendinous tissues; bone, cartilage, fat, lymphatic glands, the submucous and serous surfaces. They may arise in the internal organs: kidney, liver, spleen, thyroid glands, testis. The individual seats will be further considered under the different forms.

Structure.—The sarcoma-cell is rounded, cylindrical, spindle shaped, or of polymorphous forms, the latter usually being larger than the round or spindle forms. The large number of cells in comparison with the amount of intercellular substance is always conspicuous.



Fig. 59.—Secondary sarcomata of the lung: the primary growth was attached to the pleura.

The cells themselves contain rather large nuclei of a somewhat vesicular appearance, though sometimes quite granular and hyperchromatic. In rapidly growing tumors karyokinetic figures may be very abundant; less frequently the cells show evidence of direct division of the nuclei. Nuclear degenerations (karyorrhexis, karyolysis, and hyperchromatosis) are frequent, and doubtless cause some of the appearances supposed to be protozoa. The arrangement of the cells in sarcomata is usually very irregular; in some cases, however, particularly in spindle-celled sarcomata, the cells lie in fasciculi or parallel columns. These are the *alveolar* sarcomata. The intercellular substance consists of a homogeneous matrix with a few fibers in the case of the spindle-celled variety, but with few if any in other cases. The cells may be all of one type, but more frequently different forms or shapes occur in

the same tumor. Among the polymorphous forms of cells may be noted large flattened cells resembling endothelial plates and giant-cells resembling myeloplakes. (These forms will be discussed under the headings Endothelioma and Giant-celled Sarcoma.)

When grown in serum outside the body, sarcoma cells at first multiply more rapidly than normal ones, but soon lose this power. Irregular mitoses are seen, but direct division is not.

The blood-vessels of sarcoma are usually channels lined with a single endothelial coat (see Fig. 61), but there may be more fully developed vessels. There is growth of these imperfectly formed vessels, following, in general, the laws of new capillary development. In some cases the vascular network is very conspicuous and forms the skeleton of the tumor, the sarcoma-cells being ranged round the vessels in the form of mantles and probably springing from the adventitia. In spreading, sarcoma shows a tendency to follow vessels. It has no lymphatics and only such nerves as it encloses in its growth. Secondary changes may occur in the cellular masses surrounding the vessels, and peculiar forms of tumors thus result. (See Cylindroma.)

The general architecture of a sarcoma has a decided influence upon its character. The round-cell tumors are usually of rapid growth and the small round-cell type of the greatest malignancy among the simple sarcomata. The soft loose-textured ones are usually most malignant.

Combinations of sarcoma with other forms of tumors are not rare. All grades between the true sarcoma and the fibroma may be met with, and it is difficult to draw a line of distinction. Wherever a tendency to cellular proliferation is conspicuous and the formation of fibroblastic cells with elongated fibrous projections is not conspicuous, it is warranted to record the tumor as sarcomatous. Primary fibromata may become sarcomatous, and sarcomatous tumors perhaps at times become more benign by fibromatous transformation. Combinations with chondroma, osteoma, myxoma, and other connective-tissue tumors; with adenoma, rhabdomyoma, and fibromyoma are not infrequent. More rarely the fibrous tissue of the benign tumors may undergo sarcomatous change.

The structure of individual forms of sarcoma will be separately considered. Names have been applied to the different forms which describe the micro-anatomy, and in a sense are instructive in suggesting the relative activity and possible nature of the growth. It must not be forgotten, however, that round- and spindle-cell sarcomata both descend from the same parent cell and may be phases of differentiation.

Nature.—Sarcoma is essentially malignant. It tends to recur after removal; it affects the general health of the patient, and metastasis is frequent. Metastasis occurs through the circulation chiefly, but may spread through the lymphatics. The degree of malignancy varies greatly. The small round-celled and melanotic varieties are the most dangerous. Some forms, as the giant-celled and the fibrosarcomata, are comparatively benign. The relatively benign form of tumor, called *recurrent fibroid tumor* by Paget, is, in reality, a fibrosarcoma. The

growth of sarcomata is usually rather rapid, but shows a tendency to irregularity, and may become very rapid in consequence of irritation.

Sarcomata are injurious to the general health in some obscure way. The evidence of this is the anemia and leukocytosis and the irregular fever observed in various cases. The anemia may be trivial or severe, and may become extreme. Leukocytosis is frequent, but rarely marked. The polymorphous elements may be specially increased, but we have found the lymphocytes excessive in a number of cases. Irregular fever is often noted in lymphosarcoma and sarcomatosis. Necrotic change may increase the tendency to fever. The exact influence of sarcoma on metabolism is unknown.

Spindle-celled Sarcoma

This form may consist of either large or small spindle-shaped cells with attenuated and sometimes branching extremities, and a spindle-shaped nucleus in the small cell variety, while the large cells have an oval, bladder-like nucleus (Fig. 60). Angular or stellate cells are not



Fig. 60.—Cells from a large spindle-celled sarcoma (Ziegler).

infrequent. The cells may be ranged in parallel columns, so that the tissue becomes quite compact; and fasciculi of such cell masses may run in different directions, interlacing, and thus giving the section a fibrous appearance. In some cases the cells present no definite arrangement. Spindle-celled sarcomata are harder than the round-celled varieties and usually more grayish or flesh colored. They may be quite soft and white or degenerated and cystic.

The amount of intercellular substance in some cases, particularly of the small cell type, is quite considerable, and the term "fibrosarcoma" may be justified. The intercellular fibrils are of the fibroglia type and are indistinguishable from those of fibromata. It is very difficult sometimes to decide whether the tumor is sarcomatous or purely fibromatous. The large cell type is more cellular.

Spindle-celled sarcomata occur in the dense connective tissue of the periosteum, tendons, and fasciæ; less frequently, in the softer tissues. They are slow of growth, relatively benign, some cases showing no tendency to metastasis, though recurring after removal.

Round-celled Sarcoma

Sarcomata may be composed almost entirely of spherical or round cells, small or large in size. The designations "small" and "large round-celled sarcomata" are used, but do not really define separate varieties. The round cells when small resemble those of lymphatic organs. There is little intercellular substance. The blood-vessels may be quite large

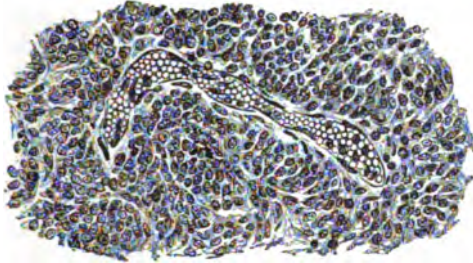


Fig. 61.—Small round-celled sarcoma: in the center is seen a blood-vessel with its wall of endothelium.

and hemorrhages with secondary changes may occur (Fig. 61). The larger cells contain relatively more protoplasm, frequently several nuclei, and not rarely different forms of cells (spindle shaped and polymorphous) are associated.

The naked-eye appearances of round-celled sarcomata are usually quite characteristic. They are milky-white, gray, or pink in color;

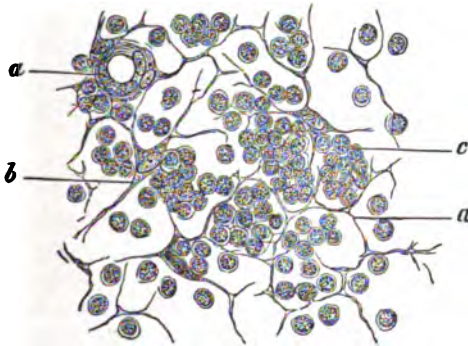


Fig. 62.—Lymphosarcoma of nasal mucous membrane: *a* on left side, a blood-vessel; *a* on right side, reticulum; *b*, cells of reticulum; *c*, sarcoma-cells (Ziegler).

sometimes quite soft or cheesy in the center, and a milky liquid exudes. Cystic changes and even calcification may occur in the center. The small-celled variety is, as a rule, softer than the larger, though both are soft.

Round-celled sarcomata are always malignant, the small-celled form being perhaps the most malignant of all varieties.

Lymphosarcoma is a variety of round-celled sarcoma. The appearance is the same as that of the other forms, but, microscopically, a close resemblance of structure with that seen in lymphatic glands is discovered. The principal characteristic is the reticulum or stroma formed by branching stellate cells united by their prolongations. In the meshes of this reticulum lie lymphoid round cells (Fig. 62). The stroma may not be plainly visible unless sections are shaken to dislodge the cells from the reticulum. The lymphosarcoma cell has a rather large round eccentric nucleus surrounded by a basophilic granular protoplasm. The distinctions of lymphosarcoma from lymphadenoma have been discussed under the latter heading. The principal feature of differentiation is the tendency of lymphosarcomata to extend beyond the normal limitations of the gland or other structures in which they originate, whereas lymphadenomata are confined by the glandular capsule.

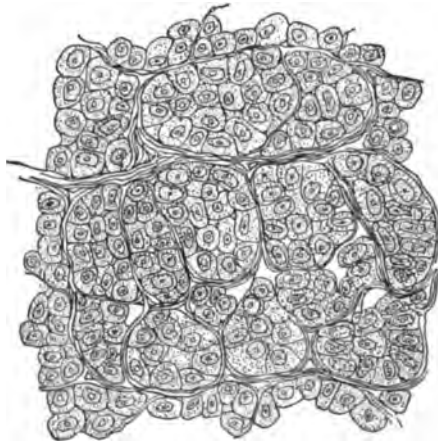


Fig. 63.—Alveolar sarcoma (Warren).

Alveolar sarcoma is a subvariety of round-celled sarcoma, though there are always spindle cells as well. It is distinguished by the occurrence of structures suggesting acini and filled with large round cells having a more or less decided epithelioid appearance. The stroma forming the acini is composed largely of spindle-shaped cells with a certain amount of fibrillar intercellular substance (Fig. 63). The blood-vessels supplying the tumors traverse these trabeculae. The round cells within the alveoli may vary greatly in size, though they are usually large. The macroscopical appearance is not specially distinctive; many of the cases, however, are pigmented (see below). Alveolar sarcoma is most frequent in the skin, where it springs from moles and warts. It may also occur in the lymphatic glands, the serous membranes, and other parts.

In some cases the alveolar appearance of the sarcoma is due to the fact that the sarcomatous proliferation has occurred in the adventitia

of blood-vessels, forming a plexus. In this way the meshes of the vascular plexus become filled with round cells and the alveolar appearance results. In other cases the alveolar character is due to the occurrence of sarcomatous foci of circumscribed character in a connective tissue. These in their growth push the connective-tissue elements aside and thus form alveolar structures.

Giant-celled Sarcoma

This variety is characterized by the presence of large multinuclear cells resembling exactly the myeloplakes of bone. The remaining portions of the tumor may be spindle celled or round celled; perhaps more frequently round and spindle cells are associated. The giant-cells are often exceedingly large and contain several or many nuclei in

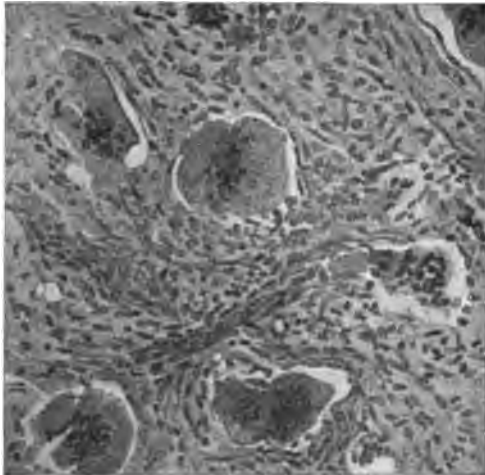


Fig. 64.—Giant-celled sarcoma (Warren).

the center of the cell (Fig. 64). The formation of these cells is most likely due to rapid nuclear multiplication. In some cases they would seem to be caused by obliteration and transformation of capillary blood-vessels; but the theory that they result from a fusion of cells seems unwarranted. Ziegler and others maintain that the presence of giant-cells does not form an essential characteristic of a peculiar type of tumor, but that it is accidental, resulting from continued irritation. The occurrence of giant-cells in sarcomata of bones would then be explained by the constant irritation of the bony particles, while in other cases the presence of masses of blood-pigment in the sarcoma accounts for the development of giant-cells in the vicinity. This view is supported by considerable authority and seems reasonable.

Giant-celled sarcomata occur most frequently about bone, and the terms *osteosarcoma* (a term to be avoided for this growth) and *myeloid*

sarcoma have been given in consequence. They may, however, occur in other situations. Their nature is usually benign, metastasis being rare.

The giant-celled sarcoma of bone is usually rather slow in growth, and gives rise to hard and irregular tumors, firmly attached to the bone structures. It may begin within the bone as a *myelogenous form* (Fig. 65) or from the periosteum. Secondary myxomatous or other change may cause more or less softening. The bone most frequently involved is the maxilla, the tumor known as *epulis* (sarcoma springing



Fig. 65.—Myelogenous osteosarcoma of the tibia (modified from Kast and Rumpel).

from the gums or alveolar processes) being generally a giant-celled sarcoma.

The *true osteosarcoma* is a more definitely neoplastic process involving a growth of young, irregular connective-tissue cells with imperfect bone formation. There may be giant-cells, but they do not dominate the field as in the tumor just described. There may be several kinds of cells in the osteosarcoma. Such tumors are definitely progressive and malignant, as against the less active giant-cell myeloid tumor above. With their growth they absorb bony tissue, and lay down new atypical osseoid material. They may be cartilaginous, or chondro-osteosarcomatous, or any combination of bone, cartilage, and sarcoma. The various kinds of cells found in sections of this tumor indicate alterations in cells natural to bone, either taking part in the sarcoma or being modified by the new growth. Thus one may find cells resembling adult bone

or cartilage cells and sarcoma-cells. When growing within a bone these tumors thin the shaft so that the thinned-out bone gives the



Fig. 66.—Bony structure of osteosarcoma of tibia.

“egg-shell crackle.” The more cellular and less bony, the more malignant is the tumor, and vice versa (Fig. 66).

Melanosarcoma

Melanosarcoma, melanoma, chromatophoroma, or pigmented sarcoma is a form in which the tumor presents a dark color on account of the presence of black or brown pigment. The latter, according to careful chemical studies of Berdez and Nencki, contains no iron, and is, therefore, not a simple blood-pigment, but melanin, a product of cell metabolism. Iron-containing pigment has been found in some tumors, and sometimes in true melanosarcomata, being found outside the cells and probably accidental, the result of hemorrhagic extravasations. The true melanin pigmentation occurs in the cells, in the cellular prolongations, or the intercellular fibrils. It is most frequently present in

the form of brownish-black granular matter, or may occur as a diffuse stain.

Melanosarcoma most commonly arises in the skin, especially in pigmented moles or warts, in the choroid coat of the eye, or in the pia mater. The growth is found to consist of cells of various shapes, sometimes round or irregular, sometimes spindle shaped, but there is a very constant tendency, especially in the pigmented sarcomata of the skin springing from warts, to assume an alveolar arrangement. In these, the cells around the periphery of the alveoli are more or less spindle shaped, while those in the center are large, irregular, or rounded cells, sometimes epithelium-like. Melanotic sarcomata of the choroid are

composed very largely of cells having an elongated character with drawn out extremities. These resemble the normal pigment cells of the choroid coat.

Melanosarcoma is extremely malignant, recurring when removed and frequently causing extensive metastasis (Fig. 67). The latter involves the local lymphatic glands in the first place, but later various organs, especially the liver. The metastases may be of the same structure as the original growth, but sometimes non-pigmented metastatic growths occur in association with the pigmented ones. Occasionally the secondary deposits are more pigmented than the primary growths. The melanoma originates from the pigment-containing cells or chromatophores of the part in which they originate. In the skin these are found in close association with the lower layers of the epidermis, and

some authors have insisted that they are essentially epithelial in origin and that the tumors should, therefore, be considered as carcinomata. There is, however, considerable ground for believing that the chromatophores are invariably connective-tissue cells. Melanosarcoma is a definite growth and not merely a sarcoma that happens to be pigmented.

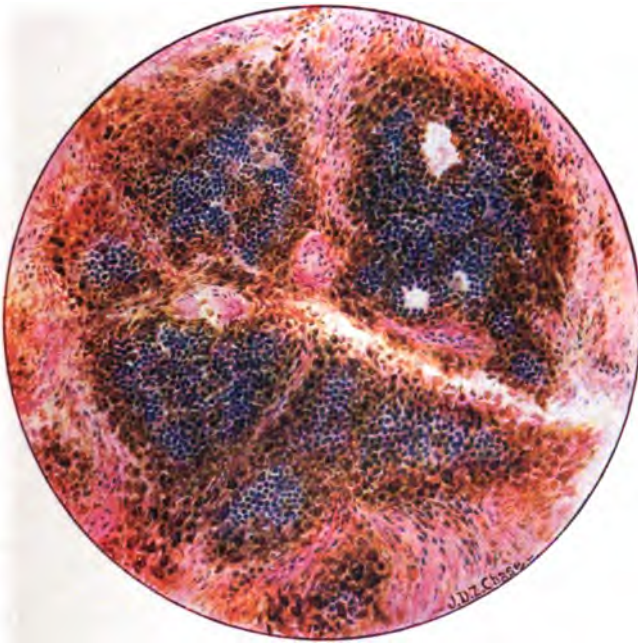


Fig. 67.—Metastatic melanosarcoma of lung, showing pigmented and non-pigmented nodules (from a specimen in the possession of Dr. Allen J. Smith).

MIXED TUMORS

All forms of connective-tissue tumors may be associated one with another; association of several forms are known as mixed tumors. Very frequently there is more or less sarcomatous tissue in such growths. With this will be found myxomatous, fibromatous, chondromatous, or

PLATE I



Melanosarcoma.

osteomatous elements. The various constituents of the tumor are arranged with no special order, but simply present themselves as masses of cells or intercellular substance of different forms combined to make a heterogeneous tissue. Among the frequent seats of such mixed tumors the parotid gland and the testicle are most important. A not infrequent combination is that of sarcomatous and adenomatous tissue. Tumors of this character are supposed to develop from embryonal "rests," and are particularly common in the kidney, where they often reach large sizes. (See also Teratomata.)

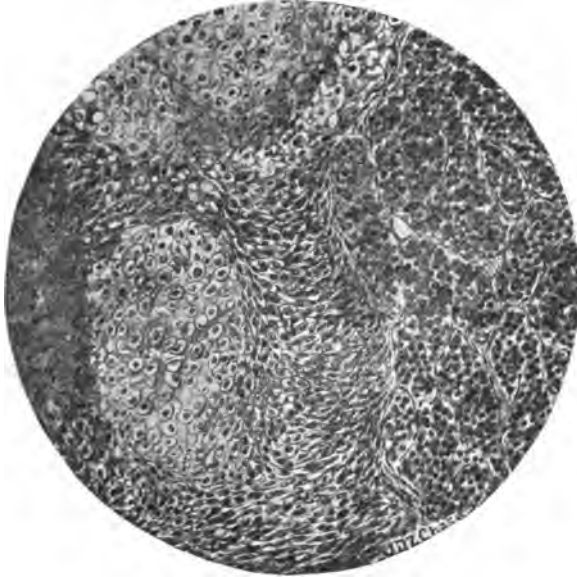


Fig. 68.—Mixed tumor of thyroid gland.

Adrenal "rests" in the kidney give origin to the Grawitz tumor or hypernephroma, a tumor largely composed of cells resembling adrenal cells, arranged in adenomatous fashion. (See Tumors of Kidney.)

Mycosis Fungoides

Mycosis fungoides or granuloma fungoides is a pathological condition of the skin and subdermal structures, having certain resemblances to sarcoma and to some of the infectious inflammations.

Etiology.—Very little is known regarding the causes of this disease. Various bacteria, principally micrococci, have been discovered in the lesions, but none of these has been shown to be pathogenic. A few observers have found bodies resembling protozoa; but it is not certain that these were really animal organisms.

Appearance.—The disease frequently presents distinct stages. First, the skin becomes somewhat swollen and red and presents eczema-

tous lesions. In some cases the appearance is that of an erysipelatous inflammation. In the next stage nodular elevations occur, and finally tumors of considerable size, sometimes as large as an orange, and more or less fungoid in appearance. Necrosis is frequent and watery or bloody liquid is discharged. The tumors may have an angry, red appearance, and have been likened to tomatoes. Rapid disappearance and reappearance of the tumors is a peculiar feature.

Any part of the body may be affected, and usually the lesions are multiple.

Structure.—Microscopically, the structure of the tumors is allied to that of lymphadenomata. There is a proliferation of connective-tissue cells about the blood-vessels and glands at the base of the papillæ of the skin, forming a network or reticulum in which round (lymphoid) cells are embedded. The cells, however, may be irregular in form and size. Mitotic figures may be found. Early in the disease the new-formed cells degenerate considerably, but later proliferation predominates, and the tumor results. The epithelium covering the growth may be thinned to a single layer, or it may show thickening. In the latter case enlarged papillæ dip down into the round-cell collections and the sections have somewhat the appearance of carcinoma. Epithelioid cells and giant-cells may occur. The tumors are poorly supplied with blood-vessels, and to this is attributed the tendency to central necrosis. Inflammatory infiltration (polymorphous leukocytes) is not observed to any considerable degree, excepting in the latter stages around and in the areas of necrosis. Mast-cells are often abundant.

Associated Conditions.—In some cases enlargement of the lymphatic glands, liver, and spleen has been observed, and has suggested the term *pseudoleukemia cutis*. Occasionally the blood presents leukemic characters.

Nature.—The disease presents many resemblances to sarcoma or lymphadenoma, and it has frequently been described as multiple sarcoma of the skin. In other respects it is allied to the infectious inflammations, though there is much less evidence of true inflammatory infiltration than in these. The relationship to leukemia and pseudoleukemia is unsettled.

Angiosarcoma

The angiosarcomata are growths depending upon a proliferation of endothelium and an expression of the tendency of these cells to make new vessels. The tumors arising in lymph-channels are called lymphangio-endothelioma or lymphangioma, while those in blood-vessels are called hemangio-endothelioma, or simply angiosarcoma. In the second variety the sarcomatous proliferation may begin in the adventitious coat of blood-vessels (*perithelioma*).

Angiosarcomata are met with in the serous membranes, in the skin, and especially in the salivary glands. Very rarely they occur in other parts of the body. The tumor is, as a rule, quite vascular, but may not be strikingly so. Sometimes telangiectatic change in the blood-vessels is

noted. Histologically these growths are characterized by round-celled masses surrounding the blood-vessels. The origin of the cells from the adventitia may be evident or obscure. In cases in which a vascular network is involved and each vessel has a coating of sarcoma-cells a plexiform appearance or arrangement results (*plexiform angiosarcoma*). In other instances in which a network of vessels is involved the sarcoma-cells accumulate in the vascular meshes in the form of cell-nests, and thus give rise to an alveolar form (*alveolar angiosarcoma*). Such forms occur in sarcomata springing from moles or warts. They are prone to melanotic change. The endothelium of the vessel is also the point of origin of vascular sarcomata. The proliferation of the endothelium leads to increase in vessels, narrowing of the lumen by irregular fibrosis.

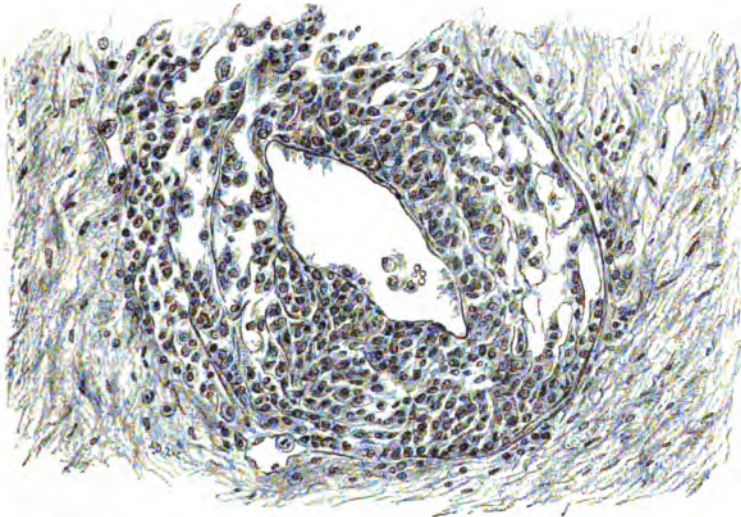


Fig. 69.—Angiosarcoma with myxomatous degeneration (cylindroma): the figure represents one of the blood-vessels with the sarcomatous cells springing from its walls, and outside of these myxomatous tissue.

Sometimes the original adventitia remains about the same size, but the lumen is filled with endothelium.

The angiosarcomata are liable to degenerations, chiefly myxomatous (Fig. 69) and hyaline, and thus a certain proportion of the cases of cylindroma (see below) have their origin. The blood-vessels may give way and hemorrhagic infiltration results.

Angiosarcomata are, in a measure, benign, metastasis being very rare in the ordinary forms. The alveolar and melanotic varieties are highly malignant.

Lymphangiomata are moist, gray, soft, spongy growths, commonest in the spleen. They are, however, quite rare. They consist of proliferated lymph-channels with well-marked swollen endothelial lining cells.

Cylindroma

This term was originally applied by Billroth to tumors showing gelatinous masses or trabeculae traversing their substance. Histologically different forms of growths may be distinguished. We deal here only with *sarcomatous cylindromata*.

The latter may be simply sarcomata in which hyaline or myxomatous degeneration has occurred in more or less insular fashion, or in which sarcoma and myxoma are peculiarly combined. Nearly always there is some hyaline change with the myxomatous. In most cases it is the angiosarcomata that present this peculiar condition. The sarcoma-cells surrounding the blood-vessels become converted into hyalomyxomatous tissue or cause the formation of this. There result branching

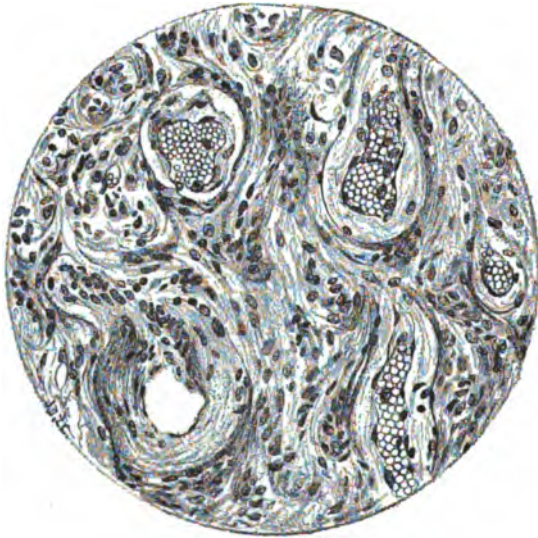


Fig. 70.—Cylindroma showing pronounced hyaline degeneration of the walls of the blood-vessels.

columns of hyalomyxomatous character traversing the sarcoma. In some cases the walls of the blood-vessels themselves may be the seat of hyaline change (Fig. 70), the proliferated sarcoma-cells surrounding the vessel being merely pushed aside. The term *angiosarcomata myxomatodes* is given to these vascular forms. Cylindromata occur in the salivary glands, the brain, the lacrimal glands, and rarely in the subcutaneous tissues. In nature they are more or less benign.

We have grouped in the following pages those tumors now believed to be sarcomatous alterations of the covering and lining of blood- and lymph-vessels. These tissues are derived from the mesoderm, as is the case with tissues giving rise to sarcomata, and resemble these tumors in their manner of growth. The individual cells approach, however, the epithelial or carcinoma type.

ENDOTHELIOMA

This tumor, which is also sometimes designated *endothelial cancer*, resembles cancer very closely in histological appearances in some cases. It affects the pleura, peritoneum, and membranes of the brain most frequently, but may be found in the skin, walls of the blood-vessels, periosteum, bone-marrow, lymphatic glands, gums, ovary, testicle, liver, and salivary glands. The serous membranes when affected become greatly thickened, tough, and white in color (Fig. 71), and irregular elevations or nodules may occur. Metastasis is infrequent, but the adjacent organs are sometimes involved, and occasionally more



Fig. 71.—Endothelioma of pleura: the pleural cavity was distended with effusion and the lung was compressed and invaded by secondary nodules.

distant structures. Endotheliomata of the dura mater spring from the inner surface of that membrane and have a flattened nodular character. Histologically they may present the concentric whorls of cells and calcification characteristic of *psammomata*.

Histologically endothelioma is characterized by more or less tubular or acinus-like aggregations of endothelial cells. The latter vary in character from those which are distinctly endothelial to the most differentiated, which may be almost typical cylindrical epithelium (Fig. 72). Between these cellular columns or acini the connective tissue of the part affected may be seen in a normal state, though it is more frequently thickened by proliferation, and may grow into and around cell groups

to such an extent that they seem admixed or that the tumor cells degenerate. In the endotheliomata of serous membranes inspection of the sections shows that the columns of epithelioid cells occupy lymph-channels, and it may be possible to demonstrate that the endothelium of the latter has been the starting-point of the cellular proliferation. In cases of carcinoma with penetration into the lymphatic channels it is notable, on the other hand, that the endothelial lining of the channels is uninvolved. Endotheliomata may in rare cases originate in the endo-

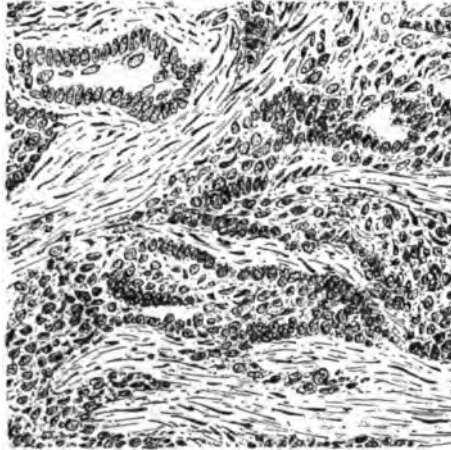


Fig. 72.—Microscopical section from the case shown in Fig. 71.

thelium of capillary blood-vessels. In these growths anastomotic channels lined with endothelial cells or anastomosing columns of endothelial cells proclaim the origin from vessels.

Psammoma

This represents no distinct species of tumor growth, but rather a peculiarity of different kinds. The name refers to the presence of calcareous matter like that of the brain-sand (*acervulus cerebri*), and psammoma has sometimes been called *acervuloma*. The calcareous matter occurs in the form of rounded masses or concentrically arranged whorls. The tumor elements themselves may be fibromatous, gliomatous, sarcomatous, endotheliomatous, or even adenomatous or carcinomatous. In most instances it is endotheliomata that present these appearances. Psammomata are met with in the membranes of the brain, the choroid plexus, and the pineal gland.

TUMORS FROM NERVE TISSUES

The various elements of adult nervous tissue are the descendents of the ectodermic cells lining the neural canal of the embryo. The tumors arising in nerve tissues contain the different elements in varying grade of differentiation, and the tumors are usually named from the

state of development. Naturally, the gangliomata and those containing chromaffin cells are of a higher grade than the tumors composed of abnormally proliferating simple nerve-cells, a very rare occurrence, or of glia. The ganglionic growths and those of some structures like the adrenal medulla, whose genesis is closely associated with the nervous system, frequently contain cells whose protoplasm stains granular brown when fixed with chrome salts (*chromaffin cells*).

The glioma when pure is a well differentiated tumor, and is of sufficiently frequent occurrence and clinical importance to warrant separate treatment. Glia tissue plays an important part in most neuroblastomata.

GLIOMA

Definition.—The term “glioma” is applied to tumors composed of neuroglia with incompletely differentiated cells and many glia fibrils. It is difficult to draw a sharp line between the circumscribed tumors of this structure and the diffuse neuroglial hyperplasia or gliomatosis met with in certain cases. (See section on Diseases of the Nervous System.)

Etiology.—It is probable that congenital defects of development play some part in the causation of these tumors, particularly in the forms more frequently spoken of as gliosis.

Appearance.—A typical glioma is usually a solitary tumor, rounded in outline, though its limits are difficult to determine, as it merges gradually into the surrounding nervous tissue. Gliomata are somewhat harder than the normal brain substance, and often the color is a little different, either more grayish or pink or reddish. Sometimes they are quite vascular and dark red. The normal shape of the part may be little disturbed, or there may be indefinite elevation. In size the tumor varies up to masses as large as a lemon. Diffuse gliomatosis causes a swelling of the affected parts, sometimes quite regular, at other times irregular. When the spinal cord is affected its thickness may be considerably increased. On section, the area of gliomatosis is rather firm and grayish in color. Nearly always there is a tendency to excavation or cyst formation. In the cord this leads to the development of considerable cavities, as a rule communicating with the central canal.

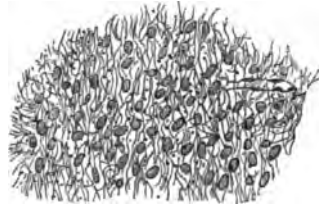


Fig. 73.—Glioma of the corpora quadrigemina (Perls).

Seats.—Gliomata occur in the brain and less frequently in the spinal cord. In rare cases the cranial nerves have been involved (Fig. 73). In one case a glioma was found over the coccyx and sacrum, originating from the remains of the lower end of the neural canal. Glioma of the eyeball will be referred to below. Diffuse gliomatosis is particularly common in the cord. It is usually met with in the vicinity of the cavities of the brain or cord.

Structure.—The minute structure of glioma varies considerably according to the type of neuroglia represented. In the typical glioma the cells contain rounded or oval nuclei, and the protoplasm is scanty. Polynuclear cells may occur among the glia elements. The glia cells possess great numbers of exceedingly fine fibrils attached and separate from the interstitial fibrils. Wavy intercellular fibrils (neuroglia fibrils) lying parallel to the axis of the cells to which they belong are characteristic structures. They are not prolongations of the cells, but merely touch the cells at their sides, the extremities of the fibrils being free. These fibrils are distinguishable from the finer fibroglia fibrils of connective-tissue growths. The abundance of the fibrils varies in different gliomata, but is generally a rather marked feature. The more rapid the growth, the fewer the fibrils. These give the section a granular appearance when seen under low magnification. In other cases the cells are of the ependymal type, and occasionally they may be arranged around the blood-vessels in rosette-forms. These formations, however, constitute only a small part of the structure, the bulk being composed of round glia-cells. The number of cells and the density of the intercellular network vary greatly. As a rule, the cells are larger than the normal neuroglia cells, and sometimes they contain several nuclei. The tumor is generally quite vascular, and occasionally telangiectatic vessels may be observed. Secondary hemorrhages are prone to occur in the latter case. Softening may occur, and occasionally sarcomatous transformation has been described, though with doubtful propriety. Embryologically the glia is an epithelial structure, and gliomata should, therefore, be classified as epithelial tumors, and sarcomatous transformation is improbable.

Diffuse gliomatosis has similar microscopical appearances, though the tissue is likely to be more compact and less vascular. In the spinal cord the process begins as a subepithelial proliferation of the glia at the posterior raphe of the central canal, the lining epithelium of this, at the same time, undergoing a certain amount of proliferation. Subsequently the gliomatosis increases and cavities form within. These may be lined with epithelial or epithelioid cells which are occasionally ciliated. Gliomatosis in the brain or cord may also present itself in the form of scattered nodular hyperplasias of the neuroglia.

Nature.—Glioma is essentially benign. It is dangerous mainly on account of the pressure it exerts. Active proliferation and eccentric growth may occasion a considerable local malignancy in some cases. It is these that were formerly described as cases of sarcomatous transformation. The growth of the tumor is rather slow. They do not seem to give metastasis outside of the nervous system.

Glioma of the Retina.—This tumor is a primary one of the retina, but may later extend to the eyeball and along the optic nerve. It is composed of round cells with large nuclei, often arranged around blood-vessels in a way suggesting the structure of angiosarcoma. This appearance is due to the fact that the cells surrounding the blood-vessels are preserved, while those at a distance are degenerated. In addition to the

round cells, there are often found cells resembling epithelium in their appearance and their arrangement, the latter being that of epithelial rosettes. Ganglionic cells have occasionally been discovered. The cells resembling epithelium have been regarded as derivatives of the outer layers of the retina, and the term *neuro-epithelioma* has, therefore, been applied by some authors. Others regard it as a glioma in the strict sense of the word. In either case the origin of the tumor is undoubtedly ectodermic, and the growth must be classified among the epithelial tumors. It occurs most frequently in children, particularly in early life (two to four years), and often on both sides simultaneously. Family predisposition, in some cases, is very striking. Extension along the optic nerve or externally, and a tendency to recurrence after removal, indicate the malignant character of the growth.

Glioma Ganglionare

Definition.—This term indicates a form of mixed tumor composed of neuroglia and nerve-fibers with large ganglionic nerve-cells; also called neuroma ganglionare.

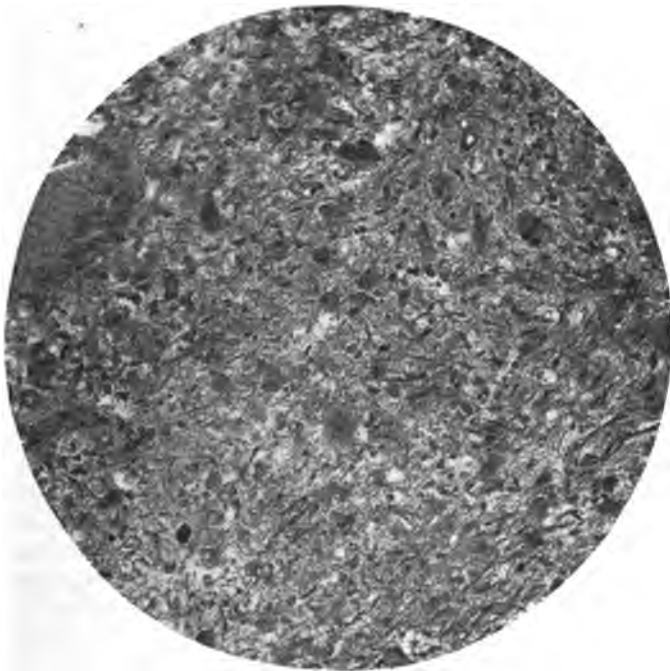


Fig. 74.—Ganglio-glioma of corpus callosum. Note the large irregular, imperfect ganglion cells, the deeply staining round glia nuclei with large wavy hypertrophic fibrils.

Etiology.—Probably congenital abnormality of development furnishes the groundwork for the subsequent development of these tumors.

Appearance.—A ganglionic glioma may resemble the ordinary glioma, occurring as a solitary tumor, the outlines of which are difficult to distinguish from the surrounding tissue. More frequently it occurs in the form of multiple nodular condensations scattered through the brain or cord. The contour of the affected parts may not be altered, and on section the growths may be recognized only by the light-colored patches and areas of increased density. A few cases of ganglionic gliomata of the spinal or sympathetic ganglia have been described. In these cases the tumors appear as rounded enlargements of the affected ganglia. Occasionally the nerve-roots are seats of these tumors; the suprarenal capsules may also be affected.

Structure.—The definition indicates the usual structure. The glial fibrils are generally conspicuous in number, the nuclei being comparatively few. Traversing the tumor there may be more or less abundant nerve-fibers with or without medullary sheaths. Large ganglionic cells may be found in considerable abundance or in small number. The vascularity of the growths differs greatly.

Nature.—The nature of these tumors is the same as that of the ordinary glioma.

NEUROMA

Definition.—Strictly speaking, neuroma is the term applied to tumors composed of nerve-cells and nerve-fibers. Ordinarily, however, the name is given to fibrous growths springing from the perineurium or endoneurium of nerves. The terms *true* and *false neuroma* distinguish between the two forms. True neuromata are rare, but Wright has called attention to the true neurocytoma or neuroblastoma made of cells like those of sympathetic ganglia associated with delicate fibrils. The last do not stain like neuroglia tissue. The cells are small, with round, deeply staining nuclei and relatively little protoplasm. They frequently assume a rosette- or acinus-like arrangement.

Etiology.—Very little is known regarding the causation. Injury may play a part, as in the case of amputation neuromata.

Appearance.—False neuromata occur as nodular thickenings along the course of nerves. They may be fusiform or elongated, may extend considerable distances along the nerves, and may form networks of ridges or elevations when the peripheral nerves are involved (plexiform neuroma). As a rule, they are multiple, and sometimes occur in exceedingly great numbers, scattered over the entire body or involving a single part of the body, as the nerves of the arm or leg. After amputations rounded thickenings may occur at the ends of the nerves and cause painful conditions of the stump.

Seats.—The peripheral nerves are most frequently involved, but the nerves may be implicated near their roots, or the terminal fibers within the organs may become affected.

Structure.—Ordinary false neuroma consists of fibrous tissue in the form of reticular connective tissue with greater or less abundance of cells pushing aside or surrounding the nerve-fibers proper.

The latter are prone to degenerate in consequence of the pressure. Proliferation of the nerve-fibers has sometimes been described, but it is doubtful whether such actually occurs. More probably the existing fibers increase in length and form a mass by curling at the end.

True neuromata of two kinds are described: those composed of medullated, and those consisting of non-medullated, nerve-fibers. The former are called *myelinic*; the latter, *amyelinic*. "Neurosarcoma" is a modified neuroma in which atypical unrestrained proliferation occurs with a markedly inconspicuous interstitial tissue. In some the proliferated cells are of the epithelioid type. These tumors may occur in the cord. Occasionally a suggestion is given of acinus-like arrangement, and to this has been given the name "neuro-epithelioma."

Nature.—Neuromata are painful tumors, but benign in a pathological sense. Their growth up to a certain point is often rapid.

LEIOMYOMA

Definition.—Leiomyoma, or myoma *lævicellulare*, is a tumor growing from smooth muscle-fibers. Nearly always there is a certain amount of fibrous tissue associated, and in the most common form, myomata of the uterus, there is always considerable fibrous tissue, and the term "fibromyoma" is appropriate. Occasionally a few unstripped muscle cells may be seen in tumors of other kinds.

Etiology.—Some of the myomata of the uterus exhibit glandular acini in the interior, which suggest their origin from congenitally misplaced portions of the Wolffian body or duct of Müller. These misplaced structures are assumed to cause an irritation of the surrounding muscle cells. This, however, is by no means certain. In other cases there are features suggesting that irritation is the important cause, though this also remains to be proved.

Appearance.—Leiomyomata are usually rounded growths, varying in size from minute nodules to huge solid masses weighing as much as 60 to 70 pounds. The largest (heaviest) solid tumor ever seen by us was a degenerated fibromyoma weighing 80 pounds. Leiomyomata are surrounded by a capsule more or less well developed and are generally quite hard, though secondary degeneration at times alters the consistency, making the tumor quite soft in the case of mucoid transformation, or stony hard when calcification has occurred. On section through the growths the stratified or fasciculated arrangement of the cells is visible to the naked eye. Concentric layers may be apparent, or a more wavy irregularity may be seen. They are grayish or flesh colored, or in rare instances quite red (*myoma cavernosum*), in consequence of enlarged vascular channels. Central softening may lead to cystic change (*myoma cysticum*).

When the myomata spring from the submucous or subserous tissues they may become polypoid, hanging from a point of attachment by a narrow pedicle. In rare instances the latter is severed and the tumor becomes a free body. Submucous myomata of the uterus may thus

eventually be discharged after a spurious labor. Subserous myomata may become free in the peritoneal cavity.

Gross myomata of the uterus may have three situations—submucous, subserous, or interstitial. Originally, all true forms begin as interstitial. In the latter the tumor occupies the wall of the uterus without any particular projection on either surface. Uterine myomata are usually multiple, occur during the third and fourth decades of life, continuing their growth until the menopause, and usually decreasing after that epoch. They endanger life by their pressure and by the copious uterine hemorrhages which they occasion. Very frequently salpingitis is associated, and recently attention has been called to degenerated conditions of the myocardium in patients suffering from uterine fibroids.

Myomata of the skin occur in younger patients, even in childhood, and are generally multiple and often painful (*tubercula dolorosa*).

Seats.—The common situations are the uterus, the gastro-intestinal tract, and the ovaries; the less common seats are the walls of the blood-

vessels, the skin, and the nipple. In all situations the tumor springs from pre-existing unstriped muscle-fiber. In most cases, according to some authors, the origin is in the walls of the minute blood-vessels, but direct origin from the muscular layer of the affected organs, or from the *erectores pilorum* in the case of the skin, cannot be denied. Myomatous metaplasia of the connective tissue, as in the case of myomata originating in the areas of old pleural thickening, has been assumed, but is improbable.



Fig. 75.—Leiomyoma.

Structure.—Microscopically, the tumor presents a characteristic appearance. Bundles of muscle cells are seen running in different directions. Those cut longitudinally show cylindrical nuclei as the most conspicuous feature, the outlines of the cell being indistinct (Fig. 75). The protoplasm stains well with eosin. Lying between the muscle cells are collagen and so-called myoglia fibrils, the latter being coarse lines lying along the sides of the cells, while the former are more delicate and are associated with fibrous tissue cells. The picture of a leiomyoma is often suggestive of sarcoma, but may be distinguished by the greater regularity in direction of the cells in different bundles and by the more distinctly cylindrical outline of the nucleus. The cells of leiomyomata may be isolated by maceration of the sections in 20 per cent. solution of nitric acid for twenty minutes, or in 30 per cent. solution of caustic potash for fifteen minutes. They are spindle-shaped structures containing a nucleus about one-third the length of the entire cell. On section they

can be differentiated from fibrous tissue cells by showing an appreciable amount of protoplasm around a rod-shaped nucleus, while the connective-tissue cell has very little protoplasm about a short spindle-shaped nucleus. Considerable elastic tissue is found in some leiomyomata, especially in the younger areas.

Leiomyomata are generally poor in blood-vessels, but may show a telangiectatic condition of the vessels. The lymphatic channels may similarly dilate, forming cystic spaces containing spontaneously coagulable material.

Of the degenerative changes, calcification is the most common, particularly in the uterine fibromyomata. This begins in the center of the tumor, but may eventually involve the whole mass. Myxomatous change may occur in myomata containing much fibrous tissue, and sarcomatous transformation has been described, but is rare.

The sarcomatous change has been explained by some as a metaplasia of the muscle cells, by others as arising from fibroblasts. The latter is probably correct. Many so-called sarcomata coming from smooth muscle tumors are doubtless merely actively proliferating, therefore softening, leiomyomata.

Uterine myomata do not all present the same appearance. Some are all of muscular nature, some are wholly fibrous, and we have all possible intermediate grades. Those in which fibrous tissue preponderates may be called "fibroids." Young tumors are mostly muscular; old ones, mostly fibrous. Whether this is purely a metaplasia or an overgrowth of the muscle by fibrous supporting tissue is not settled. The origin of the myomatous tissue is said by some not to be the uterine muscle bundles, but the muscularis of blood-vessels. The vessels of myomata have very wide walls with wide muscular coats.

Adenomyoma of the uterus is a myoma with structures like gland acini. These are variously explained as coming from remains of the Wolffian body or Müller's duct, from the mucous glands, or inversions of the serous covering. They may undergo carcinomatous increase, but adenomyomata are not malignant *per se*.

Nature.—The nature is eminently benign. Myomata of the digestive tract may cause occlusion or strangulation, or by their weight may exercise serious traction. Uterine myomata are dangerous in the ways already indicated. The growth is usually slow.

RHABDOMYOMA

Definition.—Rhabdomyoma, or myoma striocellulare, is a tumor containing more or less striped muscle-fiber. Usually there is but a small quantity of the latter, the bulk of the tumor being of some other tissue, most frequently sarcomatous.

Etiology.—Congenital defective development seems an important cause, as the tumors occur in early life and in situations in which striped muscle-fiber does not normally occur.

Appearance and Seats.—The rhabdomyomata of the kidney (the most frequent seat) present themselves as large rounded or irregular masses, more or less encapsulated. In the testicle they are similar, though of smaller size. A few cases have been described in which irregular tumors of the retroperitoneal tissues have contained muscle-fibers.

Structure.—The microscopical appearance is usually that of a spindle-celled sarcoma, containing more or less striped muscle-fibers. These are elongated spindle-shaped cells, partly striated, and suggesting embryonal muscle-tissue and rarely more fully developed muscle-fibers. Large areas of the tumor may contain no muscle-fiber at all, while certain portions are richly supplied. Adenomatous elements are not rarely associated. The tumors of the kidney which contain striped muscle-fibers are, in the main, sarcomatous or adenosarcomatous.

Nature.—These tumors are malignant in proportion as the sarcomatous element is predominant. This sarcomatous nature is indicated by activity of proliferation, spread, and metastasis. Metastasis is, however, infrequent. General cachexia and hemorrhages reduce the vitality and lead to fatal termination.

EPITHELIAL TUMORS

This heading covers all the tumors in which the cellular unit is the epithelial cell of covering or glandular tissues, supported by more or less connective tissue, the relations of the two determining the character of the growth. In some arrangements there is simply an exaggeration of the normal, the so-called typical epithelial growths, while in others there is wholly new or atypical arrangement of the elements. The first, like papilloma, are essential benign, while the second group is best exemplified by the malignant carcinoma.

PAPILLOMA

Definition.—The term “papilloma” indicates a tumor arising from a surface and covered with epithelium somewhat as the epidermis caps the papillæ of the corium.

Etiology.—It is difficult to draw a line between certain papillomatous growths that are the result of chronic irritation and others that arise in a seemingly spontaneous manner. It would appear that irritation is an important factor in most, if not all, cases, but there is also, no doubt, some form of predisposition. Whether this resides in structural peculiarities or not is difficult to determine. A peculiar form of inflammatory growth resembling the spontaneous papillomata is that known as *venereal wart*. It occurs about the genitalia or anus and especially after gonorrhea. Another form of inflammatory papillomata is that found in the mucous membranes surrounding carcinomata or chronic ulcerations of syphilitic or other kinds (Fig. 76).

Appearance.—The most familiar form of papilloma is that which occurs in the skin and which is commonly called *wart*. Warts or pap-

illomata may be single, but more frequently occur in groups, and there may be many growths in widely scattered areas of the body. A wart may be simply a smooth hemispherical elevation, or it may have a cauliflower appearance. The epidermis covering it is, as a rule, somewhat more granular or rough than that of the normal skin. The size of these growths varies from minute points to nodules as large as a walnut. On the mucous surfaces, especially where the epithelial covering is columnar, the papilloma presents itself as a soft and more distinctly cauliflower growth (Fig. 77). It is red in color, or, if the epithelium is stratified and squamous, grayish or pink. The growth is usually comparatively hard when covered by squamous epithelium.

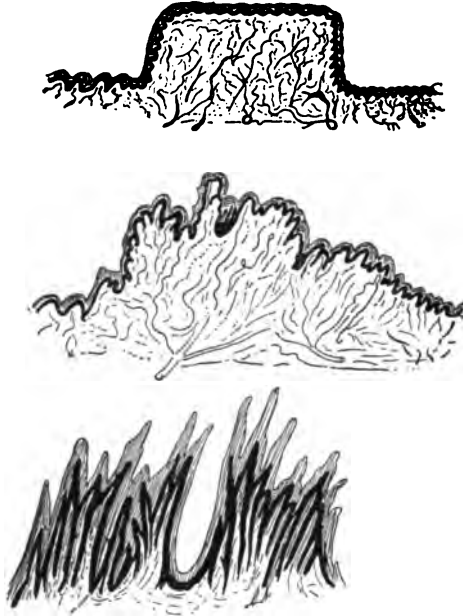


Fig. 76.—Various grades of warts and cutaneous papillomata (Perls).

Two varieties are sometimes distinguished: the *hard papillomata*, such as those which occur in the skin; and the *soft papillomata*, or the form usually seen in the mucous membranes.

Seats.—Papillomata occur in the skin of the neck, hands, back, and other parts, and in the mucous membranes, particularly in the bladder, larynx, nasal chambers, and gastro-intestinal tract. Small papillomatous outgrowths may spring from the lining membrane of glandular ducts, as in the breast or ovary. These may lead to subsequent cystic change in the organ, or they may arise after cystic change has begun by proliferation of the lining membrane of the cyst. In a similar manner papillomatous elevations may occur within the cavities of cystic adenomata (see below).

Structure.—The essential parts of papilloma are the center or groundwork of connective tissue containing blood-vessels and the epithelial covering. In the skin the growth imitates the normal papillæ, all portions of the latter, however, being greatly exaggerated, and the papilla with its covering of epidermis being raised above the surface instead of having its usual seat below the surface with the epidermal covering level with the surrounding parts.



Fig. 77.—Papillomata of the vocal cords (from a specimen in the Museum of the Philadelphia Hospital).

When there is tendency to cauliflower appearance the papilloma shows a branching form on vertical section. Each of the branches contains a connective-tissue framework with an epithelial covering. The latter consists of stratified, squamous cells and shows a decided tendency to horny change. Distinct concentric whorls of horny epithelium, such as occur frequently in epitheliomata of the skin, may be met with in papillomata. In some cases the amount of connective-tissue groundwork in the papilloma is excessive; in others the new growth consists almost entirely of proliferated epithelium. In some of these latter cases the resemblance to epithelioma

may be quite suggestive, but a distinction can be made by observing that the tumor tends to grow outward rather than into the deeper



Fig. 78.—Finer details of papilloma, showing connective stalk and stratified squamous epithelium.

structures, and always shows some connective-tissue stroma at least. The papillomata of the mucous membranes differ according to their

situation. In the larynx and other portions covered with squamous epithelium they may present much the same appearance as that seen in the skin, though the epithelium, as a rule, remains softer. There are cases, however, in which a distinct pachydermatous change is found in the epithelial covering of papillomata. In the gastrointestinal tract and in the bladder papillomata are prone to be soft and villous in appearance and are covered with a scantier epithelial coating. Cystic change is not unusual as a result of degenerative processes or of distention of the mucous glands. Occasionally hemorrhage occurs from papilloma, particularly of the villous variety. Melanotic pigment is sometimes found in warts.

Nature.—The nature of these tumors is benign, but they may be destructive of the general health in consequence of repeated hemorrhages or by interfering with the function of the organ or part in which they are situated. In some cases they are supposed to become malignant, but this has not been definitely proved.



Fig. 79.—Papilloma of the scalp. The branching fibrous stroma is covered by an abnormally thickened, irregular epithelium (Boyce).

ADENOMA

Definition.—This is the term applied to a new growth corresponding more or less in structure with compound epithelial glands, and, therefore, presenting acini or tubules containing glandular epithelial cells (cylindrical or polyhedral) growing upon a basement-membrane, and a reticulum of connective tissue and blood-vessels. It is difficult to separate from true adenoma simple glandular hyperplasia on the one hand and carcinoma on the other. This will be discussed in referring to the structure.

Etiology.—The causation of adenoma is obscure. In some cases congenital misplacements of tissue-elements appear to play a part, as is seen in the cases of adenomata of the kidney having the structure of suprarenal bodies. These tumors which, it is true, some authorities refuse to consider as adenomata, have a general resemblance to adenomata and spring from remnants of suprarenal tissues embedded in the kidney substance. Traumatism may be a factor in the etiology by exciting the proliferation of such misplaced tissue elements. In other cases the ordinary glandular structures seem to be stimulated to

abnormal hyperplasia and tumor growth in consequence of continued irritation. Instances of this sort are frequently seen in the gastrointestinal mucous membranes, notably in the stomach and lower part of the colon, in certain cases of chronic gastritis and old dysenteries.

Appearance.—The appearances of adenomata vary greatly with their seat. On the mucous surfaces there may be a simple thickening or more or less diffuse and irregular elevation of the surface, or in other cases distinct papillomatous outgrowths and rarely definite nodular tumors. In some of these cases the condition is purely one of inflammatory hyperplasia; in other cases there is undoubted tumor growth. No sharp demarcation can be established. In the substance of the organs adenomata occur as nodular tumors, usually singly and well circumscribed, and not rarely surrounded by a fibrous capsule. They are moderately firm, and on section whitish or pink in color. Sometimes cystic change occurs as the result of dilatation of the glandular acini or in consequence of degenerative softening; in these cases the consistence is correspondingly altered.

Seats.—Among the situations in which adenoma is frequent may be mentioned the mucous membranes, the skin, and certain organs, notably the mammary gland, liver, kidney, suprarenal bodies, thyroid gland, and ovaries. Clinically important seats are the pylorus, the duodenal papilla, the rectum, and the uterus. In these situations adenomata spring from the epithelial tubules or mucous glands. In the skin the points of origin are the sebaceous and sweat-glands.

Structure.—The definition in general indicates the structure of these tumors. They are more or less typical; that is to say, there are acini of normal appearance presenting a single layer of columnar epithelium, with perhaps in places a tendency to heaping up the several rows of epithelial cells. In the simple adenomata there is usually one layer. The greater the number of layers of epithelial cells, the greater the tendency to malignant growth; such a condition is found in adenoma malignum along with other features. The acini are well inclosed by a surrounding connective-tissue reticulum, and the appearance of normal gland tissue is thus produced. Unlike normal glands, there are no excretory ducts, or, at most, imperfectly developed ducts.

Two varieties of adenoma are sometimes distinguished: the tubular and the racemose or alveolar. In the former the glandular system is simple and consists of tubular formations lined with columnar epithelial cells; in the latter the appearance is that of more complicated glands with closely aggregated acini of circular outline containing columnar and often cubical or polyhedral cells. The number of varieties may be carried further, however, for in the liver the adenomata resemble the normal liver structure rather than the ordinary glandular formation above described. In the suprarenal capsules and kidney the appearance is that of slightly atypical suprarenal structure, or in other cases that of embryonal renal tubules distended to form considerable cystic spaces, with partitions and inwardly projecting papillomatous elevations.

With the further growth of adenomata the appearance may be little

changed. In some cases considerable variations occur, and there is a tendency, more marked in some situations than in others, to active proliferation of the epithelium, which may cause a considerable alteration in the histology of the tumor, and eventually transformation into definite carcinoma. The terms "adenocarcinoma," "destructive adenoma," and "malignant adenoma" are sometimes applied in such cases. The same names, however, are given to a type of adenoma characterized by the formation of abundant anastomosing or separated tubules and acini with comparatively little reticular tissue, and by the tendency to repetition of the same structure in the local extensions from the original growth and even in metastases (Fig. 80).



Fig. 80.—Destructive adenoma (Beyea).

The connective-tissue stroma of adenomata may be moderate in quantity or may be considerable. In some adenomatous proliferations of the mucous membranes the number of gland acini or tubules may be relatively small, while the interglandular connective tissue shows active round-cell infiltration to a very considerable degree. Sometimes the interglandular tissue is distinctly sarcomatous (adenosarcoma). In other instances the bulk of the tumor may consist of connective tissue of fibrous character in which are embedded a relatively small number of glandular alveoli. In all of these cases it is difficult to determine whether the connective-tissue process was primary and the epithelial secondary, or the reverse.

As has been suggested, it is well-nigh impossible to distinguish between some adenomata and some hyperplasias. This is particularly true of hyperplastic growth without fibrous tissue. This condition is, however, apt to follow the general architecture of the gland in question and is not apt to be encapsulated. The adenomata have a tendency to show small, normal sized, and cystic acini in the same field. It is like-

wise a task to differentiate chronic inflammation and fibro-adenoma. In the former nearly all gland tissue is compressed and cysts are rare. When present they soon lose their epithelium. In fibro-adenoma epithelial reduplication is pronounced and the fibrous tissue increase is more diffusely distributed.

Secondary changes are common, the adenomata of the stomach and uterus being particularly prone to change their character to that of carcinoma. In these cases there may be noted active proliferation of the epithelial cells, so that acini or alveoli become completely filled, or that the ends of tubular structures become blocked up. There is a tendency to extension of epithelial infiltration beyond the limits of the acini, cancerous outgrowths being the result. In other cases the

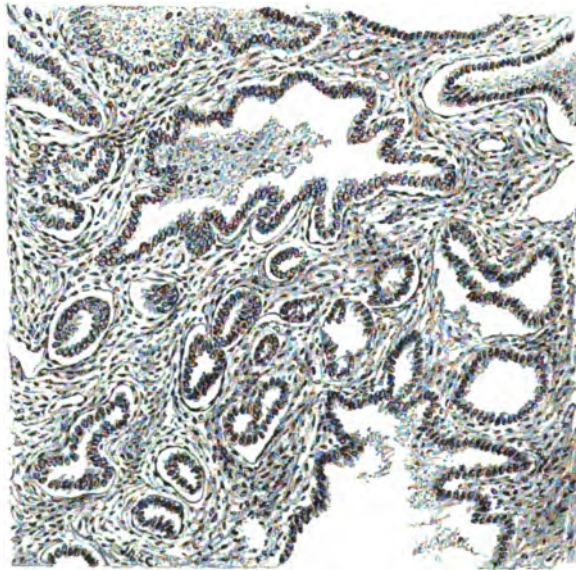


Fig. 81.—Adenoma of the mammary gland, with cystic enlargement of acini and abundant interglandular hyperplasia of connective tissue.

malignancy is manifested by the excessive epithelial proliferation in the form of new acini of irregular character (see Fig. 80). Eventually the tumor may become purely carcinomatous; in other cases, however, it continues to increase in size, always retaining its adenocarcinomatous appearance, but never becoming typically carcinomatous.

Degenerative changes may be met with in adenomata as in other tumors. Hyaline transformation or production of hyaline or myxomatous tissue in the stroma may give the tumor an appearance justifying the term "cylindroma" or "cylindro-adenoma." Such cases are rare. Myxomatous and even calcareous change may sometimes be observed. The connective-tissue stroma may proliferate actively and assume sarcomatous appearance—adenosarcoma. Cystic change may result from

gradual dilatation of the glandular acini or from distention of normal ducts or alveoli of the gland in which the tumor occurs. In these cases the terms "cystic adenoma" or "cystadenoma" are applicable (Fig. 81).

Nature.—Adenomata are benign tumors. In some cases, however, a pure adenoma may give rise to metastasis. Those of the liver, for example, not rarely cause secondary deposits in the spleen and less frequently elsewhere. The adenomata of the thyroid gland similarly cause metastasis, though their structure does not in any way suggest a malignant growth. Destructive adenomata or adenocarcinomata are malignant in proportion to the amount of carcinomatous transformation on the one hand, or of atypical glandular proliferation on the other.

The effect of adenomata on the general health is variable. They do not contribute to the general metabolism as far as is known, though occasionally biliary pigmentation of the adenomata of the liver, and even of their metastases, and the secretion of milk-like fluid in mammary adenomata evidence the partial preservation of function by the cells. The general health may be unfavorably influenced by adenomata of the mucous surfaces in consequence of their interference with normal functions or in consequence of secondary ulceration and hemorrhage.

CARCINOMA

Definition.—The terms "carcinoma" or "cancer" may be applied to tumors in which epithelial proliferations in the form of solid blocks or columns, or in the form of atypical acini, separated by more or less connective tissue, present themselves, the epithelial proliferation showing a tendency to extend beyond normal anatomical limits. It is extremely difficult to construct a definition that will be universally applicable. Some have regarded the tendency of the epithelial proliferation to break through the normal limits, and extend beyond the confines of the epithelial structures from which it rises, as the important fundamental element of carcinoma. Others have held that there is a peculiar atypical character in the epithelial cells themselves, shown by irregular cell division, hyperchromatosis, and other features. The older authors believed that polymorphism and certain irregularities of cell contour suffice to distinguish carcinoma-cells from normal cells or those of other tumors; but this polymorphism is now recognized to be the result entirely of compression in the growth of the tumor, and to be, therefore, accidental. Some have believed that the term "carcinoma" should include all epithelial tumors giving rise to metastasis, but this necessarily restricts the term too greatly on the one hand, and, on the other, includes certain tumors probably purely adenomatous. We prefer to regard as carcinoma any epithelial growth atypically reproducing certain glandular or other structures and showing a manifest tendency to irregular extension.

Etiology.—The causes and nature of carcinoma are still obscure. A number of theories have been offered. These have been referred to in the discussion of the etiology of tumors in general. A brief reconsideration may be useful in this place:

(a) **Congenital Theory.**—The theory of Cohnheim regarding the etiology of tumors in general is less applicable to cancer than to certain other growths. There are a few examples, however, which would seem to prove that misplaced epithelial cells undergo carcinomatous proliferation; for example, there are cases of apparently primary carcinoma springing from bones which would seem to require this explanation. It is not always certain, however, that such cases are actually primary. The rarity of carcinomata in early life would seem to negative the congenital theory, and, at all events, would show that other influences of importance are requisite.

(b) **Traumatic Theory.**—Clinicians are inclined to give great weight to this. A single traumatism probably has little importance, though women frequently state that they recall distinct injuries from which carcinomata of the breast have seemed to originate. It must be recalled that such injuries are sustained by practically every woman, and the presence of carcinoma would readily be attributed to a preceding hurt. In cases of epitheliomata of the lip in pipe-smokers, in the carcinomata of the scrotum and limbs in chimney-sweeps and paraffin-workers, in the skin of tar workers, and in cases of uterine carcinomata following laceration of the cervix, the effect of chronic irritation would seem to be important. The frequent association of gall-stones with carcinoma of the gall-bladder has often been considered in the same light.

(c) **Infectious Theory.**—The peculiar growth of cancer, its destructiveness of the general health, and its metastasis readily suggest an infective origin. Bacteriologists sought to isolate micro-organisms without success; later investigators have turned their attention to low forms of animal life—protozoa. (For further discussion, see p. 161.) A few successful experiments have been made at implantation from man to animals, or from one animal to another; but as Hanau, one of the early experimenters in this work, himself states, these experiments do not prove infectiousness. The secondary growths in the second animal may be simply of the nature of metastasis, due to implantation of the cancer-cells, followed by their proliferation.

A renewal of activity in the study of the etiology of cancer during recent years, and with all the advantages of modern methods, has thus far led to no positive result. Statistical evidence, the probable cases of accidental infection in surgeons and others, the more or less suggestive results of experimental inoculation, and the distribution of cancer—lend some probability to the infectious theory, but it must be confessed that the evidence is far from positive.

Among vegetable organisms to which etiological significance has been attributed are the blastomycetes, which some investigators claim to have found in every cancerous growth examined, and the assumed importance of which is further based upon the results of experimental infections with cultures of the organisms. The invariable occurrence of blastomycetes has, however, been disproved, and the experimental lesions are not really analogous with carcinoma. Many inter- and intracellular cancer parasites have been described. There are within

and between the cells certain unusual bodies with rather definite staining reactions seeming to pass through a metamorphosis. These are now explained as the results of nuclear degeneration or discharge of its chromatin. Still other intracellular bodies in cancer are to be explained as the remains of ingested masses, since the cancer-cell in its progression into the surrounding tissue consumes cell detritus. None of these bodies can be held as proved causes of cancer.

(d) **Tumor Dyscrasia.**—This indefinite term is supposed to indicate that certain peculiarities of the liquids of the body occasion the tendency to cancerous growth. No proof of the existence of any definite dyscrasia has ever been furnished, though it is not unlikely that some form of disposition to this growth acts as the predisposing cause, even if traumatism, infection, or other factors are the immediate cause.

Certain conditions are supposed to precede and favor some cancers. Paget's disease of the nipple may precede mammary cancer, as also gastric ulcer may pave the way for carcinoma of the stomach. Previous benign epithelial growths may become carcinomatous, as indicated by their penetrative and greater proliferative powers, but not necessarily by any alteration of the cells themselves.

Age plays an important part in the formation of carcinoma, as this tumor is essentially one of advanced years. Among 275 cases collected by Lubarsch, 55.6 per cent. occurred between the ages of forty-five and sixty-five. There were a few instances in childhood and early life. Between fourteen and nineteen there were 1.46 per cent.; between twenty and twenty-five, 1.8 per cent.; between twenty-six and twenty-nine, 1.1 per cent. The frequency in later life was formerly ascribed to some alteration in the vitality of the epithelial cells, rendering them more liable to abnormal proliferation. The nature and cause of such alteration, however, remain obscure and theoretical, though there is certainly a greater tendency to cancer growth as age increases.

Heredity was formerly regarded as of great importance. Certainly in some cases there seems to be hereditary transmission of the tendency to develop carcinoma.

Appearance.—Carcinomata differ considerably in appearance in different parts of the body. Those of the surface present themselves as more or less nodular, flat elevations. In the skin the nodules may remain hard and rather smooth, or they may soften upon the surface, forming unsightly ulcerations. In the mucous membranes the growths are more frequently soft and polypoid or cauliflower excrescences (Fig. 82). Ulceration may occur on the surface of such elevations, or from the first the tumor may be of ulcerative character, causing spreading excavations limited by thickened projecting edges. Carcinomata of the glandular organs form more or less nodular tumors or irregular infiltrations. These vary greatly in consistency, some being almost stony hard, others soft in consequence of their preponderating cellular character or of secondary degenerations. On section, the tumor is found to be white or grayish in color, generally somewhat translucent and glistening; milky liquid may ooze from the surface. Capsule formation is rarely

seen, though in occasional instances the normal connective tissue of the organ is pressed outward by the growth of the tumor, and thus forms an imperfect capsule. The primary growth is generally solitary. Occasionally instances are observed in which two separate masses develop

simultaneously and apparently independent of each other, as in the two breasts. More frequently apparent multiplicity is caused by the early appearance and rapid growth of metastases.



Fig. 82.—Carcinoma of the duodenal papilla (modified from Kast and Rumpel).

Secondary carcinomata are nodular in character and nearly always multiple. The larger are often distinctly encapsulated. Central softening or contraction of connective tissue may give the surface of the nodule an umbilicated character (Fig. 83). The number varies greatly, from a few large or small nodules to in-

numerable tubercle-like forms in *general carcinomatosis*. In some situations, as in bones, secondary carcinoma has an infiltrating character.

Seats.—The situations in which carcinomata occur are very numerous; they invariably arise from pre-existing epithelial structures. In



Fig. 83.—Metastatic nodules of carcinoma on the surface of the liver (Hanot and Gilbert).

the rare instances in which a presumably primary carcinoma has occurred in bone or other connective tissues the presumption is warranted that the tumor originated from remnants of epithelial tissue left by faulty development. Among the frequent places of origin the most

important are the uterus, the skin, the gastro-intestinal tract, particularly the esophagus, pylorus, and rectum, the mammary gland, the ovaries; less frequently the liver, kidney, thyroid gland, prostate, or testicle may be the starting-point. Secondary carcinomata curiously do not often affect parts in which the primary growth is frequent. Of the many seats of secondary carcinoma, the lymphatic glands, the liver, spleen, lungs, heart, and serous membranes are the most important. Secondary carcinoma of the bones is specially frequent after carcinoma of the breast or the thyroid gland.

Structure.—The histology of carcinoma varies greatly in different situations and in different forms. There are two distinct elements involved—viz., epithelial cells and a connective-tissue stroma. The

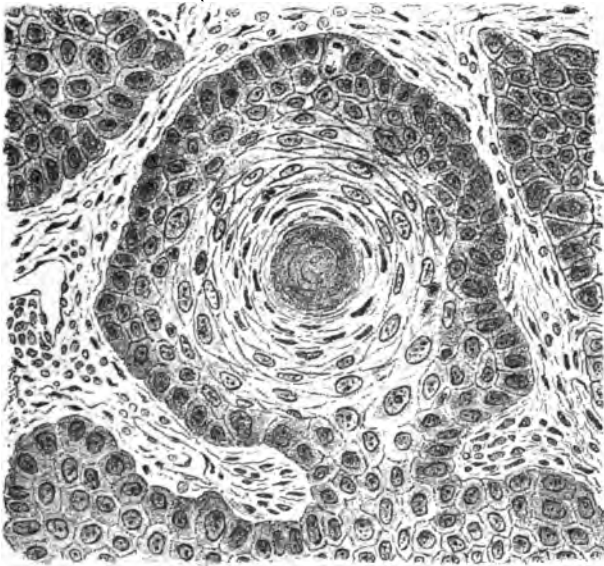


Fig. 84.—Epithelioma of skin, showing concentric arrangement and degeneration of cells.

epithelial cells are medium sized or large, and have a rather large and clear nucleus; the shape of the cell, however, differs widely. In epitheliomata of the skin the cells are large and usually of a squamous variety. In carcinomata of mucous membranes they are more often cylindrical or columnar, and there is a tendency to the formation of cuboid or polyhedral epithelium. The last-named forms are habitually present in the cancers of glandular organs. The mutual compression exercised may occasion a polymorphous character, and the older writers wrongly regarded this as a feature by which a carcinoma-cell could be recognized as such. Secondary changes may occasion wide variations in the appearance of the cells; thus, the epithelia of cancers of the skin tend to become arranged in concentric whorls and at the same time to become somewhat glistening from horny transformation (Fig. 84).

The nucleus may be clear and quite structureless, or may show a distinct nucleolus and a definite chromatin network. Karyokinetic figures may be quite abundant and are frequently atypical. Degenerative changes (dropsical infiltration, myxomatous change, fatty degeneration) may alter the nucleus as well as the body of the cell.

The epithelial cells are usually grouped as cylindrical and branching or anastomosing columns, or as irregular tubular formations, the tubules being of varying lengths. The explanation of the structure of the columns or tubules is that they are formed by the extension of the masses of proliferated cancer-cells along the lymph-channels and spaces of the tissue. Very often the section shows all the tubules cut transversely, and thus the appearance of glandular acini is given. In some cases the tubules are short and acinus-like; as a rule, however, the appearance is

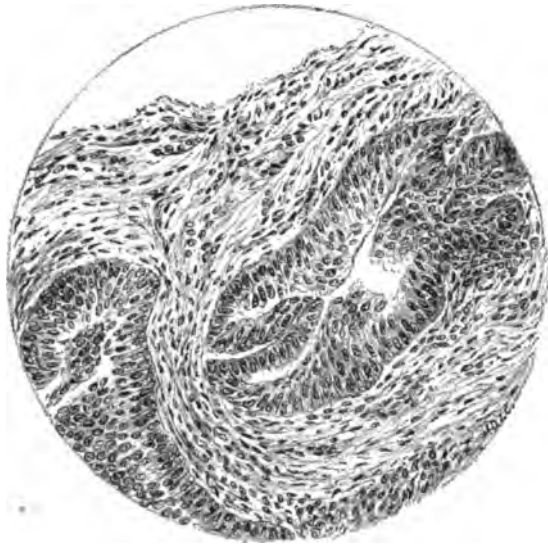


Fig. 85.—Carcinoma of uterus.

only due to the manner of section. The acini differ strikingly from those of adenoma in showing several or many layers of cells instead of one, and there is the further difference that cellular outgrowths may be seen at the periphery of the acini, the cells having broken through the retaining wall (basement-membrane) and proliferated outside to form new clumps (Fig. 85). On examination of the epithelia within the acini it is found that those of the peripheral layer frequently retain the columnar character seen in the normal alveoli of the gland from which the tumor springs.

The connective-tissue stroma of carcinoma is more or less dense, but practically is always of fibrous character. It is arranged in such manner as to form hollowed spaces or columns in which the epithelial structures already described are embedded. The connective tissue

carries the blood-vessels. The lymph-vessels probably connect directly with the cell-nests. In general, the more connective tissue in a cancer, the less its malignancy; while the more cells, the greater its tendency to metastasis and recurrence. Recently attention has been called to the fact that elastic tissue is formed in the stroma of the tumor in varying abundance. Frequently infiltrating leukocytes and plasma-cells or mast-cells are seen within the stroma. When the stroma begins to grow and show atypical proliferative tendencies we have what is called *carcinoma sarcomatodes*.

The above description applies to the ordinary carcinoma of glandular organs. Some difference is observable in the cancers of the skin and other external surfaces. In these the structure is rather that of much enlarged papillæ, the interpapillary epithelial plugs penetrating into the deeper tissues. The cells in their early stages are similar to those of the deeper layers of the skin, are larger and more translucent than those of glandular cancers. Subsequently the cells tend to become of the squamous type and undergo more or less horny change. Hollow alveoli and acini are unusual in cancers of the skin, though such structures may occur in some cases.

Degenerative Changes.—Carcinomata are quite prone to degenerations. In nearly all cases in which the tumor has reached considerable size more or less fatty degeneration of the cells becomes apparent. Preceding this or associated with it may be cloudy swelling or dropsical infiltration of the cells, rendering the nuclear outline less distinct and sometimes causing vacuolations. Irregular and multiform nuclear degenerations are met with, and probably occasion some at least of the structures known as parasites of cancer. The epitheliomata of the skin are particularly prone to a horny transformation, this occurring first and most prominently in the concentric whorls already described. In the adenocarcinomata of the ovaries and other genital organs of women the degenerated epithelial cells frequently undergo calcareous infiltration, and psammomata are thus formed. Colloid degeneration of the epithelial cells is a rare event, and the term "colloid cancer" is generally a misnomer, the real degeneration in most of these being myxomatous, affecting the connective tissue principally, though the epithelial cells are to a certain extent involved. Complete degeneration by myxomatous or associated myxomatous and fatty change may destroy all of the characteristics of the original tumor. In some cases cystic transformation occurs in organs the seat of cancer, or in the cancer itself. This may be due to occlusion and subsequent dilatation of the ducts of the organ or of the acini in the tumor, the cystic spaces becoming filled with mucoid or gelatinous material. In some instances cystic carcinomata are secondary developments originating in cystic adenomata. Hyalin change and pigmentation are rare in cancer.

Hemorrhage occurs by ulceration of a large vessel. Inflammatory processes are quite common. Cancers on free surfaces are prone to undergo ulceration in consequence of irritation and infection. Among the micro-organisms discovered in such instances the staphylococcus

and streptococcus are conspicuous. A distinct erysipelatous inflammation may occur in cancers as in other structures. Invasion of tubercle bacilli and the growth of miliary tubercles in carcinoma are rare events, though they sometimes occur. Associations of carcinoma and tuberculosis or syphilis may in other cases result from the secondary growth of cancer in pre-existing gummatous or other syphilitic lesions or in lupus. Practically all carcinomata show some leukocytic infiltration. The amount of this, however, varies greatly. In the healthy tissue bordering carcinomata there is always an inflammatory infiltration of round cells, but this does not limit the growth like a capsule. A carcinoma is probably never sharply margined.

Nature.—Carcinoma is essentially malignant, the degree of malignancy depending, however, upon the seat and upon certain peculiarities of the individual. Sometimes a small growth may remain practically latent for a long time, until accidental circumstances, like traumatism, intercurrent disease, pregnancy, or the like, stimulate active growth. Its rate of growth is variable, but chiefly it is progressive, regardless of speed. Occasionally there are remissions or even cessations, with retrogression and absorption, but this latter is rare.

Carcinoma exhibits all the elements of malignancy: the tendency to recur after removal, metastasis, and general deterioration of the health. Recurrence after removal is most readily explained upon the assumption that the entire growth has not been removed. Microscopical studies show that the area of infiltration is usually much greater than the naked-eye appearances would indicate, and this explains why the surgeon seldom removes the whole disease. Metastasis, as a rule, follows the lymphatic channels, and thus primarily involves the lymphatic glands in the neighborhood of the growth. The process may be explained as follows: Some of the epithelial cells in their advancing proliferation penetrate the lymphatic channels and are carried in the lymph-stream to the nearest lymphatic gland, where they again proliferate and form secondary nodules; from these a similar extension occurs, and eventually widespread metastasis results. Less frequently the primary growth penetrates the walls of a vein and metastasis occurs through the circulation. This is quite common in the case of cancers of the stomach or intestines. The metastatic foci first spread through the portal circulation to the liver. In still other instances secondary growths result from mechanical transportation in the movements of the body; thus, in carcinomata of the abdominal organs the peristaltic movements may transfer particles to different parts of the abdominal cavity.

Pathological Physiology.—The general health of patients suffering with carcinoma is affected very profoundly, though the manner in which this occurs remains obscure. It would seem to be of the nature of a toxemia. (See page 161.) Emaciation and loss of strength are habitual, though often, perhaps, in large part the result of interference with organic functions, as, for example, in carcinoma of the stomach. Progressive anemia may make its appearance, the red corpuscles becoming less abundant and the quantity of hemoglobin falling decidedly.

There is usually a moderate amount of leukocytosis, the large mononuclear forms increasing particularly. Toward the end of life the tissue destruction increases greatly, though the excretory products of such may not be notably increased in the excretions in consequence of failing circulation and imperfect renal function. At this stage the accumulation of such products in the blood may lead to sudden death from coma. (See Acid-intoxication.) Hemorrhages and ulcerations may also contribute to the impairment of health in cases of cancer.

VARIETIES OF CARCINOMA

There are several forms of cancer sufficiently different to require separate description. The classification of these is generally based upon the character and arrangement of the epithelium. We may distinguish (1) epitheliomata, carcinomata composed of surface epithelium, either (a) squamous or (b) cylindrical, and (2) glandular carcinomata, having either (a) more or less distinct adenomatous structure or (b) solid plugs or columns of epithelial cells, or (c) a mixture of acini and solid columns.

Epithelioma

This form, which consists of surface epithelium, is of two varieties, the squamous and the cylindrical.

Squamous epithelioma occurs in the skin or mucous membranes, where squamous epithelium exists normally. Among the frequent seats are the lips, the esophagus, the larynx, and the cervix uteri. Occasionally squamous epithelioma arises in parts normally covered by other kinds of epithelium, as, for example, in the fundus of the uterus. In these instances there is probably a primary metaplasia of the epithelium followed by carcinomatous growth. Even in carcinomata of the breast some of the acini may present metaplasia of the cells to the squamous type. Squamous epitheliomata present themselves as nodular, wart-like elevations of the skin or mucous membrane, tending to become ulcerated on the surface, with little tendency to hemorrhage. Those of the mucous surfaces are more elevated and softer. Grossly, on section, they appear as firm white or gray masses, with soft areas of cellular growth and shiny white striæ of connective tissue. Histologically there are seen branching columns of epithelial cells extending downward into a stroma, well dotted with round cells from the papillæ of the skin, into the deeper structures. These consist of large translucent squamous cells which show a tendency to arrange themselves in certain places concentrically to form epithelial *perles*, taking acid dyes well. The latter frequently undergo a horny transformation and sometimes even calcareous change (Fig. 86). The same structures occasionally occur in papillomata, but much less frequently. Metastasis is frequently seen in the neighboring lymphatic glands, but the malignancy is less marked than in glandular carcinomata.

Some authors have described as a separate form skin cancers com-

posed of cuboid or polymorphous cells resembling those of the basal layer (Malpighian layer) of the skin and their embryonal equivalents. This is the so-called *epithelioma* or *carcinoma basocellulare*. Rodent ulcer

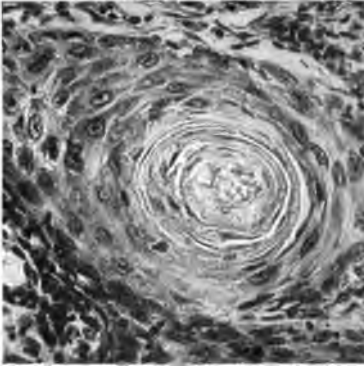


Fig. 86.—Squamous epithelioma, showing whorls of epithelial cells with central degeneration (from a photograph by Dr. W. M. Gray).

belongs to this group, and while we do not agree that this is a different tumor, it varies from the typical in having greater cellular content of polymorphous cells and a paucity of pearls. As a matter of fact, all cancers of the skin originate from the basal cells, and the special variety alluded to differs from the ordinary type only in the fact that the cells do not become transformed, as in the normal growth of skin and in ordinary epitheliomata, into squamous cells. Such forms originate from the hair-follicles, sweat-glands and sebaceous glands, as well as from the basal layer of the epiderm.

Other varieties of epithelioma have been described depending upon the shape, arrangement, and alteration in the cell-nests. The cystic epithelioma is of the basal cell type, with degeneration of cell-nests and

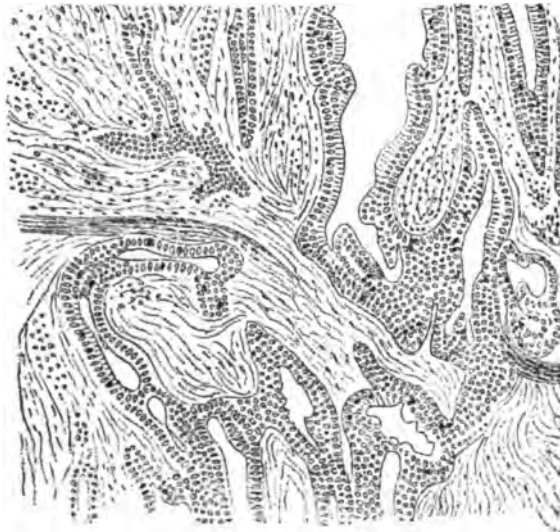


Fig. 87.—Cylindrical epithelioma of the intestine (Perls).

the formation of cysts. All such forms are but accidental modifications and have no separate place in histogenesis. The name "epidermoid carcinoma" is given to those infiltrating growths which so retain the

stratification of the epidermal layers, or which assume this arrangement when not growing from epidermis.

Cylindrical Epithelioma.—This form is composed of columnar or cylindrical epithelium. It is frequent in the mucous membranes, especially in the gastro-intestinal tract and the uterus. The epithelial cells of the tubular glands or sometimes those of the surfaces form the starting-point of the growth. More or less acinus-like tubular structures, composed of a layer of epithelial cells, or more frequently of a number of layers of epithelia, the outer layer being often distinctly columnar, constitute the characteristic feature of the tumor (Fig. 87). In the later stages the acini become filled with proliferated epithelial cells of various shapes and the cylindrical or tubular character of the lining is lost. Carcinomata of the kidney, liver, and mammary gland, though not originating from surface epithelium, strictly speaking, may be of the cylindrical form. Cylindrical epitheliomata more nearly resemble the glandular carcinomata in their malignancy and general behavior than the squamous variety.

Glandular Carcinoma

This term includes the carcinomata that have a resemblance to racemose glands in their histological structure. They consist of acini or alveoli containing epithelial cells, usually in several layers or completely filling the lumen, and a stroma of connective tissue. Some authors distinguish three forms: the *simple*, the *medullary* or *encephaloid*, and the *scirrhous*. These are simply variations of the same tumor. In the simple form there is a combination of epithelium and stroma in about the proportion seen in normal glands. The tumor is, therefore, neither strikingly hard nor soft. In the medullary or soft carcinoma the amount of epithelium is excessive and the tumor has a soft character (Fig. 88); while the scirrhous, or hard, cancer is an indurated form, due to excess of fibrous tissue and deficiency of the epithelium (Fig. 89).



Fig. 88.—Medullary carcinoma of breast.

The glandular cancers are more or less nodular or infiltrating growths, varying in consistency in different cases, but having, on section, a glistening white color with a certain amount of translucency. Milky liquid exudes from the surface on section. This is composed of albuminous fluid containing degenerated epithelium and free oil-droplets. Among

the seats in which these forms occur the most important are the pylorus and other mucous surfaces, the mammary gland, the pancreas, kidneys, ovaries, and testicles. Widespread metastasis and other features of

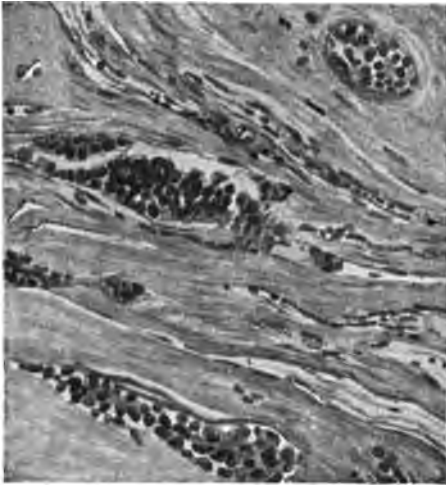


Fig. 89.—Scirrhus cancer of breast (Warren).

malignancy are noted. In the case of the scirrhus form the primary tumor may be strikingly small in comparison with the amount of metastatic deposit. We may further divide glandular cancers according to the source from which they arise or as to the general architecture they retain during the earlier stages. Thus we may speak of (1) columnar epithelial carcinoma when throughout the formative stages the long narrow cells are retained. These grow from tubular glands with cylindrical epithelium like in the intestinal tract. (2) Duct cancer when

cuboidal cells predominate and the general arrangement is tubular. (3) Acinous cancer when the acinus grouping, with more or less distinct cell-nests having a low or polymorphous epithelium, predominates.

SPECIAL FORMS OF CANCER

There are degenerations in some cancers which give them peculiar physical and chemical properties. Such alterations do not justify a

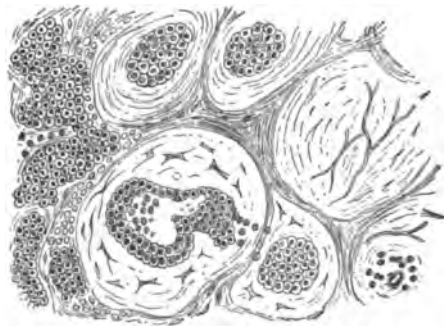


Fig. 90.—Colloid cancer of the breast, showing myxomatous change in the stroma and fatty degeneration and partial disappearance of the epithelial cells (Perls).

pathological separation, but clinically they have an importance. The most important are mucoid and colloid. In the former the interstitial tissue undergoes myxomatous change, making the tumor soft and dis-

tended with a viscid material. In colloid cancer the cells undergo the change.

The term "colloid" is usually a misnomer, as most of the colloid cancers contain no colloid material. The name *gelatinous* would be more appropriate, but has not been generally accepted. Such colloid cancers are met with in the stomach and intestinal tract, in the mammary gland, and in the ovaries. The tumor has a peculiar transparent, glistening appearance. The entire mass may be uniformly jelly-like or only portions of it are affected. Microscopically mucoid degeneration of the epithelial cells and stroma is discovered (Fig. 90). In some cases no trace of carcinomatous tissue may be discoverable, the whole tumor having undergone degeneration. Degenerative cancers frequently spread by direct extension, and the entire abdominal cavity may become filled with material representing degenerated secondary growths. Occasionally the same kind of peritoneal growths seem to originate primarily in the peritoneum; the origin of these may be fetal remnants of epithelial tissue (Fig. 91).

True colloid cancer—that is, carcinoma with colloid degeneration of the epithelium—is sometimes seen, though it is very rare. It occasionally causes a gross appearance resembling that of sarcomatous cylindroma, and the term *carcinomatous cylindroma* has been applied.



Fig. 91.—Colloid cancer of the peritoneum (modified from Birch-Hirschfeld).

CYSTS

Definition.—This term includes pathological formations of varied character. Some are true tumors; others are of quite different nature.

The term "cyst" is applied to pathological formations consisting of a more or less well-defined wall and enclosing liquid or semiliquid contents of different character from the surrounding parts. This definition is not entirely applicable, as certain structures that do not present a definite capsule are sometimes termed "cysts." Accordingly, we may distinguish between *true cysts* and cyst-like formations or *cystoids*, the former being enclosed by a capsule lined with epithelium or endothelium; the latter merely presenting a circumscribed collection of softened material.

Classification.—According to the method of formation, we distinguish retention cysts, softening cysts, cysts due to the presence of

foreign bodies, and proliferation cysts. There are also cysts which owe their origin to some faulty development *in utero*. They are in a sense teratomatous and we shall consider them under a separate heading.

Retention cysts are formed when the excretory ducts of a gland become occluded and the secretions accumulate and cause distention of the acini or of parts of the duct. Among such cysts may be named the distended sebaceous glands of the skin in the formations called *wens*; the cysts of the salivary or small mucous glands or ducts under the tongue, called *ranulae*; retention cysts formed in the uriniferous tubules, the tubules of the ovary, or in the parovarium, in the acini and ducts of the mammæ, pancreas, and other glands. An entire organ may become converted into a cyst, as in cases of distention of the kidney (hydronephrosis) from obstruction of the ureter.

These cysts are distinguished by the fact that they have a distinct connective-tissue wall lined with epithelium or endothelium. The contents of the cyst depend upon the part in which the formation has taken place.

Softening cysts occur in consequence of degenerative softening of normal or pathological tissues. They are not rarely the result of hemorrhage, the blood-clot first becoming inspissated and then serous exudation occurring in the area of hemorrhage. Softening cysts are very common in tumors of different kinds.

Cysts due to foreign bodies are, in part, softening cysts. The tissues in the immediate vicinity may be injured and undergo necrotic softening, while connective-tissue reaction produces a capsule. This form of cyst is most frequently the result of invasion of parasites, and the cyst contents may be composed of the parasite or the parasite and tissue elements more or less degenerated.

Proliferation Cysts.—This term is applied to formations more closely analogous to true tumors than those mentioned before. They merit more extended description than the other forms of cysts, and may be designated as epithelial cysts.

Epithelial Cysts

Definition.—In certain glandular organs, notably the ovary and mammary gland, cystic formations occur which present striking appearances, and, though perhaps they represent adenomatous or carcinomatous new growths, are so striking as to deserve special mention.

Etiology.—These growths, in part at least, result from obstruction of excretory ducts and subsequent irritation by retained secretions. Congenital abnormalities of structure may possibly play a part in their causation.

Appearance.—Cystomata may be single or multiple, the entire tumor being composed either of a single cyst or of one large cyst subdivided into many smaller ones; or, again, of numerous separate and unconnected cysts of varying size. On section, the cystic cavities are found to contain more or less serous or gelatinous liquid, and sometimes hemor-

rhagic fluid is observed. Most frequently the liquid is gelatinous or ropy, and is commonly spoken of as colloid material. The inner lining of the cyst may be smooth, like a serous or mucous surface, or elevated irregularly in the form of polypoid outgrowths into the cavity of the cyst. The entire cyst may thus be filled with papillomatous elevations from the epithelial lining. The term *papilliferous* or *proliferative cystomata* is given to these forms (Fig. 92). The size of cystomata varies from minute tumors not larger than a pea to enormous masses weighing as much as 60 or 80 pounds. Secondary degenerations may occur in the form of softening, hemorrhage, or calcification.

Seats.—The mammary gland and ovary are the principal situations in which tumors of this description are met with, but analogous growths may make their appearance in any of the glandular organs.

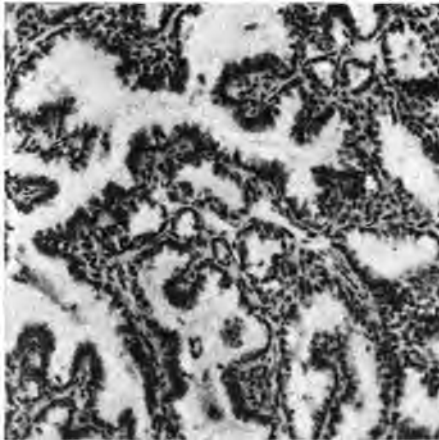


Fig. 92.—Papilliferous adenocystoma of the kidney (Karg and Schmorl).

Structure.—Microscopically, these growths present cystic cavities lined with typical or modified columnar epithelium and a stroma or reticulum of connective tissue. The amount of the latter and the appearance of the cysts themselves vary in different cases. At times the stroma is very abundant and takes the form of well-organized fibrous tissue, while the cysts and acini are small and few in number. In these cases the appearance suggests a primary proliferative connective-tissue process with secondary implication of the epithelial elements. Such cases occur particularly in the mammary gland, and there is difficulty in separating them sharply from instances of chronic interstitial mastitis or diffuse fibroma. In other instances the process manifestly begins with the formations of epithelial acini, and the hyperplasia of the connective tissue is certainly secondary. The acini in these cases present themselves as hollow spaces of varying shape and size, often branching, and lined with columnar epithelium in a single layer or sometimes with several layers of more or less well differentiated columnar epithelium.

Nature.—These cystic growths often have a decided tendency to malignancy. They may remain benign throughout; but frequently they undergo carcinomatous change and spread widely or give rise to metastasis. The malignancy is generally in proportion to the amount of the epithelial proliferation and papilliferous change, but there are instances in which metastasis occurs from adenocystomata having regular gland acini lined with single layers of typical columnar cells. The cystomata of the ovary not rarely extend to the surface of the organ, break through the capsule, and present upon the surface as papillary growths, and frequently they extend to the peritoneum and neighboring structures. The entire abdomen may be involved. At the same time, or in other cases independent of such direct extension, metastatic deposits may be seen in nearby lymphatic glands. Somewhat the same conditions may be observed in cystoma of the breast, but in this situation the tumor is much more frequently confined within the capsule of the organ.

CHAPTER VII

TERATOLOGY

THIS subject includes all those abnormalities which are due to congenital defect. Such a subject, while not exactly a part of the progressive tissue change, is ushered in here by the necessity of taking up certain tumors having a polymorphous character more or less dependent upon formative defects. Teratomata or mixed or polymorphous tumors or those due to formative defect will first be considered, and the terata will then be discussed. The word "terata" may be applied to any abnormalities of growth, but is best confined to monsters. In order to show the position of the various abnormalities we here give a short classification (Birnbau's), which also indicates in a measure what we know of the etiology:

(a) Single monsters.

- (1) Malformations due to arrest of development.
- (2) Malformations due to excess of development.
- (3) Malformations due to errors of development.
- (4) Malformations due to displacement of tissue and persistence of fetal structures.
- (5) Malformations due to fusion of several characters.

(b) Double monsters.

Two theories are given for monster formation. One is that there is some inherent fault in the germinal cell, and the other ascribes malformation to malign influences upon the developing ovum. The latter is more generally accepted. It is assumed that the damage is chiefly felt before the gastrula stage in a single ovum.

Since all organs or organ systems do not progress to their development in a regular progression, but in an irregular saltatory manner, the correct development of any one depends upon the proper mutual relations of adjacent or associated units or groups. If, therefore, the progress and restraint of one unit be removed, this allows abnormal growth in those dependent upon it. In this way one can explain headings *a*, 1-3, 5; while the double monsters are expressions of the above effects upon a doubly impregnated ovum. Twins can arise from one ovum.

TERATOMATA

Definition.—The term "teratomata" is applied to tumors of peculiar mixed character, representing different elements of complex tissues or structures in a situation in which these do not normally occur, growing typically, atypically, or both. For example, the most frequent form of

teratoma contains various epidermal structures, such as hair, teeth, etc., and occurs in internal organs. Those containing fetal tissue or abnormally placed tissue come under heading *a*, 4.

Etiology.—The causation of teratoid tumors or teratomata is to be sought in congenital misdevelopments. We may, with Klebs, distinguish *endogenous* forms in which inclusions of superficial tissues are retained in internal parts by a process of constriction; and *ectogenous* forms, in which a separate fetal deposition is the origin of the tumor. The latter form represents a separate and ill-developed fetus within the developed organism—a *fetus in fetu*. They are also called “embryomata.” A regular gradation may be traced from distinct teratoid tumors having irregular mingling of tissue elements to malformations in which a more or less systematic outgrowth, somewhat approaching double monstrosities, occurs. Of the distinct teratoid tumors, the most frequent is the dermoid cyst.

DERMOID CYST

This ectogenous tumor presents itself as a cystic formation with a connective-tissue membrane and an inner lining resembling the skin. This may present all the elements of the skin, such as stratified epidermis, a papillary layer, and even subcutaneous connective tissue. Hair-follicles and sebaceous glands are frequent, and habitually long, light-colored hairs are found within the contents, and teeth may be found in the lining membrane or free in the contents of the cyst. The cyst is filled with a semifluid, cheesy mass consisting of epithelial cells, fatty matter, and other detritus. Occasionally dermoid cysts may contain nerve tissue, muscle, thyroid tissue, or structures resembling intestine.

The dermoid cysts vary in size from minute bodies no larger than a pea to huge masses, the latter being most frequent in the ovaries. Among the situations in which dermoids occur the ovaries are most common; less frequently they are found in the testicles, in the peritoneum, in the membranes of the brain, about the eye, in the neck, floor of the mouth, and elsewhere. Growth is very slow, and they may remain practically latent through life.

The nature of these tumors is usually benign, though carcinomatous change may occur, and in the ovaries cystoma is prone to be associated, and the latter may be malignant.

Other Teratoid Tumors

Mixed tumors are terata arising from embryonal cells which are capable of a differentiation to approximate more than one type of adult tissue. They may descend from cells of one or all layers of the embryo, and may be ascribed to the power of syncytial cells to develop into an embryo, or the inclusion of one ovum in another. These are the teratomata proper, to which reference has been made, while mixed tumors

represent usually two or, at most, three types of cells. The most conspicuous examples are Wilm's congenital adenosarcoma of the kidney and adrenal carcinoma.

Nodular masses may appear about the head or neck or in various parts of the body, consisting of mingled tissues of various kinds, such as glandular tissues, connective tissues, nerve, muscle, etc. Sometimes they resemble some definite organ, as in the case of growths appearing at the umbilicus of the newborn and simulating the structure of normal intestine.

In the neck there are sometimes seen more or less cystic growths lined with epithelium and having in their walls muscle-fibers, lymphoid tissue, cartilage, etc. These growths probably spring from remnants of the embryonal branchial clefts. The mixed tumors of the parotid gland (see Sarcoma) are allied to these.

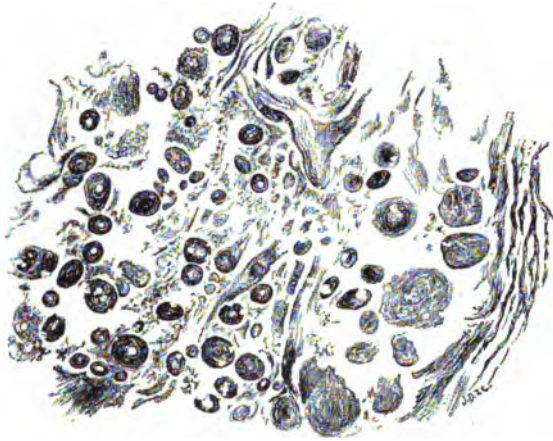


Fig. 93.—Cholesteatoma from the membranes of the brain.

Cholesteatoma.—This tumor is characterized by glistening, whitish, or pearly bodies composed of concentric layers of cells resembling epithelium (Fig. 93). Sometimes crystals of cholesterin are found in the center of these bodies, whence the name cholesteatoma. Cholesteatomata are found in the membranes or substance of the brain, and present themselves as single or multiple nodules. They are usually soft and glistening in appearance. Some authors consider them endotheliomata, but Ziegler has found hair-follicles and hairs in certain specimens, and from this, as well as from the horny change to which the cells in the pearly bodies are prone, classifies them among the teratoid growths. They probably originate in ectodermal fetal inclusions or rests.

Somewhat similar tumors occur in the pelvis of the kidneys, in the testicles, parotid glands, ovaries, and middle or external ear.

SYNCYTIOMA MALIGNUM

This term is applied to a form of tumor originating at the placental site during pregnancy or the puerperium. It has also been called "deciduoma malignum," "sarcoma deciduocellulare," "destructive epithelial tumor of the placental site," and "chorionepithelioma" (Fig. 94). It may follow a hydatid mole (*q. v.*).

The tumor occurs as a hemorrhagic infiltrating growth, somewhat resembling placental tissue in gross appearance, and frequently causes metastasis by breaking into the blood-vessels. The metastatic nodules are found in the external genitalia, frequently in the lungs, less often in the liver, spleen, or other organs. The growth is rapid, the uterine wall



Fig. 94.—Chorionepithelioma or syncytioma malignum. (By the courtesy of Dr. Barton Cooke Hirst from a painting made for him from a slide belonging to Dr. Herbert Fox.)

being quickly invaded and metastasis occurring in a short time. It has no vessels, but grows within placental blood spaces, and is prone to hemorrhage by infiltration and ulceration of maternal vessels. The cells are loosely enough arranged to separate and enter vessels to form metastasis.

The nature of this tumor is still the subject of some controversy. Two types of cellular elements are recognized in its structure. One of these consists of irregular masses of protoplasm containing dark nuclei (syncytial tissue). The nuclei probably multiply by direct division. These protoplasmic masses are arranged in islands or in branching columns which form a network. In the meshes of this network are blood spaces containing thrombi or masses of blood corpuscles. Sometimes masses like those above described are found within the

blood spaces. The second form of cells consists of smaller irregular-shaped elements, which are unusually rich in glycogen, and in which cell division by karyokinesis is observed. These cells lie in masses, of greater or less size, between and beside the larger protoplasmic areas before described. In the later stages of the growth obliterative thrombosis of the vessels leads to necrosis of the cellular constituents, particularly of the columns of large epithelium-like cells. These are converted into homogeneous fibrinous masses, and even the thrombi themselves may degenerate. The view of Marchand regarding the nature of these tumors is most widely accepted. He holds that the larger cells are derivatives of the syncytium (a structure composed of epithelial cells, probably of fetal origin), while the smaller cells are formed from the deeper epithelial covering of the chorion villi (Langhans' cells). The tumor, therefore, is epithelial in nature, and it has malignant properties. It differs, however, from ordinary epithelioma and from carcinoma in its peculiar structure and in its clinical course and dissemination.

Syncytial cells are occasionally found in tumors of the adult unassociated with pregnancy. They are supposed to be either fused cells or to have a tendency to the formation of chorionic cells, possibly from germ cells. These cells have been found in brain and testicular growths. The name "syncytial carcinoma" or "epithelioma" is given.

Terata or Monsters

We refer the student to books on normal and abnormal embryology and teratology for a full discussion of the terata. Here will be given only examples of the various headings on p. 235:

(a) *Single Monsters*.—(1) Malformations by arrest of development are exemplified by the failure of closure of the median fissure of the body or the failure of union of organs developing in both sides and intended to be one, *e. g.*, the bifid uterus.

(2) Malformation in excessive development occurs in the form of supernumerary fingers or internal organs, the spleen, for example.

(3) Malformations of error are seen in club-feet, hernia, or when the testicle is not included in the scrotum. *Hermaphroditism* exemplifies failure of fusion of sexual elements from the two sides.

(4) Malformation by displacement is exemplified by transposition of all the viscera (*situs transversus*) or of single organs, as when the heart is found on the right side. Persistence of a remnant of the omphalomesenteric duct, so-called Meckel's diverticulum, and of the *truncus arteriosus* are instances of the retention of embryonal structures.

(5) Under this heading are found fusion of esophagus and trachea, and of the two kidneys, forming a horseshoe-shaped organ.

(b) *Double monsters* are the results of superfetation, or the fusion of incompletely formed fetuses. When the two fetuses are joined together by the ventral surface they are called anterior duplications; when joined by the head, *craniopagus*; by the sacral region, *pygopagus*. When they are fused at the pelvis they are *ischiopagi*; and if the trunk

and legs are fused, leaving the head and neck free, we have *dicephalus*. *Syncephalus* means fusion of heads with the two bodies free.

The cysts of antenatal origin are mostly examples of endogenous, constriction, or inclusion cysts, or remains of fetal structures intended for removal. The thyrolingual cyst is due to failure of closure and obliteration of the thyrolingual duct. It is in the midline of the neck. Branchial cysts at the side of the neck are mucous or sebaceous collections in the remains of the branchial clefts. Persistent portions of the Wolffian body or duct may give rise to uni- or multilocular cysts of the ovary or broad ligament. Cyst of the kidney are due to imperfect development of the portion of the Wolffian body which makes the secreting part of the kidney.

CHAPTER VIII

BACTERIA, THEIR NATURE AND ACTION

History.—Although for many centuries there had existed the idea that disease and decay are due to the action of minute organisms, it was not until the use of the lens enabled the Dutch naturalist Leeuwenhoeck actually to demonstrate their presence in water and in human intestinal contents that the hypothesis of a “contagium vivum” became more than mere guesswork. He discovered, even with his imperfect instruments, short rods, curved and straight, and described their motility. Müller (1785), by the use of the compound microscope, attempted a more systematic classification of these micro-organisms, and from that time many investigators have added much to our knowledge of microbes, that group of organisms which had been denominated by Linnæus by the term “chaos.” To the German Henle is due the credit of having first introduced an idea of order into this disorder. He held that fermentation was the result of organic life, and that the action of a contagium was analogous to that of a ferment. The earliest systematic experimental work was that of Pasteur, in which he established beyond doubt this relation between fermentation and the life and development of bacteria. The first definite ideas of the physiology of these micro-organisms are found in his experiments on lactic-acid fermentation, and the pathogenesis of micro-organisms was established by his demonstration of the etiology of the silkworm disease (1869). Davaine and Rayer about the same time established the causal relation of a bacillus found in the blood of a sheep dead of anthrax to that disease.

CLASSIFICATION

Bacteria (schizomycetes, or cleft fungi) is the name given to a branch of the lowest and simplest of the orders of the vegetable kingdom. They belong to the class *Thallophyta* and order Schizophyta or Schizomycetes. Other orders of this class are unimportant except the Eumycetes, comprising the moulds and yeasts. They are small, unicellular organisms, generally free of chlorophyl, and colorless; they possess a cell-membrane albuminoid in composition, and homogeneous protoplasmic cell contents. They range in size from a fraction of a micromillimeter up to 40 μ . Some varieties are motile. Nuclei are absent, though in the opinion of some the whole body may be regarded as a nucleus. Bacteria multiply by cell division, sexual distinctions being absent. In many species resistant bodies—spores—occur.

Many classifications, all of them being to a certain extent artificial, have been made by different authors. Probably one of the most useful and scientific is that of Migula, as modified by Chester:

Schizomycetes

- I. **Coccaceæ**.—Spherical cells dividing in one, two, or three directions. Endospores rare.
 1. *Streptococcus*.—Division in one direction, the individuals cohering to form chains. Motility absent.
 2. *Micrococcus*.—Division in two directions, the individuals when coherent forming groups of four. Flagella absent.
 3. *Sarcina*.—Division in three directions, forming packets of eight, increasing in geometrical ratio. Motility absent.
 4. *Planococcus*.—Division in two directions, as in the micrococcus. Motility present.
 5. *Planosarcina*.—As the sarcina. Motility present.
- II. **Bacteriaceæ**.—Rod-like, cylindrical cells, dividing at right angles to the long axis.
 1. *Bacterium*.—Cells without flagella, often with spores.
 2. *Bacillus*.—Cells with peritrichous flagella, often with spores.
 3. *Pseudomonas*.—Cells with polar flagella, spores rare.
- III. **Spirillaceæ**.—Cells cylindrical, curved, bent, or spiral. Division as in II.
 1. *Spirosoma*.—Cells rigid, without flagella.
 2. *Microspira*.—Cells rigid, with one, rarely two or three, polar flagella.
 3. *Spirillum*.—Cells rigid, with five to twenty polar flagella.
 4. *Spirocheta*.—Cells flexible, motile, but without flagella; perhaps possessing an undulating membrane.
- IV. **Chlamydobacteriaceæ**.—Cells united in a simple unbranched filament. Division in one direction. Forms non-motile; conidia.
 1. **Mycobacteriaceæ**.—Short or long cylindrical units or filaments, clavate, cuneate, irregular, or regular in form; may have false or true branching. No spores. Gonidia bodies may occur; non-motile; transverse division; no sheath.
 - a. *Mycobacterium*.—Short cylindrical, bent cuneate. May show true branching.
 - b. *Actinomyces*.—Long branching filaments, gonidia, end organs, dry growth (very close to next genus, Streptothrix).
 2. *Streptothrix*.—Cells united in a simple unbranched filament. Division in one direction. Forms non-motile; conidia, true branching.
 3. *Cladothrix*.—Cells united in a filament, with a false branching.
 4. *Crenothrix*.—Cells united in an unbranched filament, and dividing in three directions into small rounded cells.
 5. *Phragmodithrix*.—Cells at first united in an unbranched filament, and dividing in three directions. Later the separate cells break through the thin membrane and grow out as branches.
 6. *Thiothrix*.—Cells united in an unbranched filament contained in a thin membrane. Division in one direction. Cells contain granules of sulphur.
- V. **Beggiatoaceæ**.—Cells united in a filament without sheath. Motile, the movement being due to an undulating membrane.

Eumycetes

True fungi are of some pathological importance in skin diseases and occasionally in general infections. The classification is given of the most important genera. This is one of the orders of the Thallophyta.

1. Suborder Phycomycetes.
Family Mucorinæ, Genus Mucor.
2. Suborder Hemiascomycetes.
Family Saccharomycetaceæ, Genus Saccharomyces, Subgenus Blastomyces.
3. Suborder Euascomycetes.
Family Aspergillaceæ, Genus Aspergillus, Genus Penicillium, Genus Oidium.

The simple elementary forms that occur are of three kinds: the coccus, the bacillus, and the spirillum (Fig. 95).

Coccus.—This is a spherical cell, varying in size up to $1\ \mu$ in diameter. It takes the anilin stains readily. Spore formation and motility are rare. When the cocci are found in groups, the individuals being entirely separate, they are termed staphylococci, from the resemblance of the groups to a bunch of grapes; when in pairs, diplococci; when in chains, streptococci; when in groups of four, tetrads, or merismopodia; when in packets, sarcinæ.

Bacillus.—A rod-shaped, cylindrical cell of varying length and thickness. Spore formation and motility are common. Most of the group



Fig. 95.—Various forms of bacteria: 1 and 2, Round and oval micrococci; 3, diplococci; 4, tetrads; 5, streptococci; 6, bacilli; 7, bacilli in chains, the lower showing spore formation; 8, bacilli showing spores, forming drumsticks and clostridia; 9 and 10, spirilla; 11, spirochetes.

stain easily with the anilin dyes, but some require special methods of staining.

Spirillum.—A cylindrical, rod-shaped cell, curved or spiral, sometimes motile. It stains readily.

MORPHOLOGY

Cell Contents.—The body of the organism in unstained conditions appears as a perfectly homogeneous protoplasmic mass. On staining with anilin dyes a granular appearance is often observed, which under high powers is resolved into a hyaline mass containing numerous chromophilic granules. Vacuolations also are often present. Some observers (Bütschli *et al.*) have made out a network immediately within the membrane and surrounding a central body which readily stains with the nuclear dyes. This latter they regard as a nucleus. Others, however, affirm that this appearance is due to a concentration of the cell protoplasm (endoplasm), the result of the rather complicated method of staining. The question of the presence or absence of a nucleus is still an open one. In many organisms, as the diphtheria bacillus from a blood-serum culture, for example, there exist certain transparent refractive bodies which stain differently from the rest of the microbe. These metachromatic bodies, as they are called, are regarded by Ernst as nuclear in character. Others look upon them as possibly the primary stage of spore formation.

Most authorities today merely accept that a bacterium has both chromatic and cytoplasmic parts, and do not insist that the large central area staining by nuclear methods is a definite nucleus. Some of the chromatic bodies seem to have the power of growing out into a full rod when freed from the parent rod into favorable media (Kneass).

Spore.—The spore is a non-vegetative resistant form that the microbe assumes when the conditions for growth are unfavorable. The endoplasm seems to concentrate and become a small oval, highly refractive body, separated from the bacterial protoplasm by a membrane of its own. It is generally of the same diameter or somewhat smaller than the bacillus itself, and is situated either in the middle (equatorial) or at the end of the microbe (polar spore). It may be larger in diameter than the microbe and cause a swelling at that point. When in the center of the rod this gives rise to the form known as clostridium; when polar, to the so-called drumstick form (as in the *Bacillus tetani*).

The spore is extremely resistant to conditions to which the vegetative form readily succumbs; to the action of certain chemical reagents, light, heat, etc. Bacteria that are grown on media poor in nutrient material tend to become asporogenous. A certain temperature is also necessary for spore formation. Thus, although the anthrax bacillus develops well at a temperature of 14° C. (57° F.), it does not form spores below 18° C. (64° F.). To obligate anaërobes oxygen is necessary for their development, and aërobic cultures present them in the absence of that gas. Placed under conditions favorable to its vegetation the spore loses its clearness, absorbs water, and swells. A small prominence presents at the side or end, which gradually lengthens and develops into a young bacillus. The membrane of this new microbe is formed from the inner layer of the spore membrane (*endosporium*), while the outer layer (*exosporium*) is cast off. In not all of the varieties of bacilli does sporulation take place, and even where it does occur there may, under certain conditions, as in growth at high temperatures, arise races which have lost this power (asporogenous races).

The spore does not stain readily with the ordinary anilin stains, and special methods have been devised for coloring it.

The polar or Babes-Ernst granules are condensations of endoplasm which stain by particular methods. They are due to the chemical reactions of the medium upon which the organisms are growing. Their biological importance is small, but they assist in identification at times.

Cell-membrane.—Surrounding each organism is a membrane (*ectoplasm*) denser and more highly refractive than the cell contents (*endoplasm*). In most cases this is not to be differentiated from the endoplasm; but in a few it is larger, and under certain conditions becomes a gelatinous mass. In this case it is easily seen, especially after appropriate staining. This is called the *capsule*. In general, this occurs only when the bacteria develop within the animal organism, and not upon artificial culture-media. It is probable that the ectoplasm is not a mere protective envelope, but has to do with the functional activity of the bacterium. The fact that the flagella, to which is due the motility of certain microbes, are directly continuous with and are simply prolongations of this membrane, points to this view.

The cell-membrane is not easily colored by ordinary methods.

Flagella.—Motility is often a property of bacteria. It is manifested in different ways, and is often characteristic of special varieties of bac-

teria. Some move slowly forward across the field; others, with great rapidity; others, again, dart hither and thither, slowly or so quickly as to be with difficulty observed. They may at the same time have a rotary movement around their long or their short axes.

After appropriate staining the cause of this motility is seen to be the presence of slender, whip-like prolongations, originating directly from the ectoplasm (Babes). They may be twenty times as long as the body of the bacterium, and are arranged in the different species in different ways. Bacteria that possess no flagella are termed "gymnobacteria"; those that have these organs, "trichobacteria." There may be but one flagellum, situated at the pole (*monotrichous*), or a number may be present (*lophotrichous*). When they are situated at both poles the microbe is termed *amphitrichous*; when distributed over the whole body of the bacteria, *peritrichous*. The presence and the activity of flagella depend on many factors: on the condition of the medium, bacteria grown on liquid media being more active than those on solid; on temperature; on presence of air; on light; and on the age of the culture. They are easily broken off from the microbe, and care must be used in staining them.

Involution Forms.—By involution form is meant the irregular appearance a microbe often assumes when its conditions of growth are unfavorable. Numerous bacteria melt together and become irregular chains, or they appear pear or club shaped. The protoplasm becomes retracted and irregular staining takes place. Sometimes forms with branching projections are discovered. These have often been described as involution forms, but are now more commonly regarded as normal, though unusual, structures. This applies to tubercle bacilli, diphtheria bacilli, and some others. This true branching (dichotomy) must not be confounded with false or pseudodichotomy due to mere apposition of separate organisms, as seen in various bacilli, streptococci, etc., and habitually in the cladothrices.

Chemistry.—The bacterial cells are of variable composition, depending to a great extent upon the kind of nutrient matter. They consist mainly of water (85 per cent.). The chief solid material is albumin. This varies according to the medium of growth, and has been given the general name of *mycoprotein* (Nencki). Fat is also present. The nucleic bases—xanthin, guanin, adenin—and cellulose have been found by some. Some contain certain coloring-matters, bacteriopurpurin, and a green substance similar to chlorophyl. Organic acids and ferments of different kinds are also found. In some special forms—the sulphur bacteria—sulphur is present.

BIOLOGY

Bacteria may be divided into two great classes: those that live only on dead organic matter are termed *saprophytes*; those that develop in and at the expense of the living organism, *parasites*. These latter by their growth cause certain pathological conditions in the host, and are called *pathogenic*. By *obligate* saprophytes or parasites we mean those that

can exist only under the conditions named; by *facultative* saprophytes or parasites, those that can develop under either condition.

Conditions of Growth.—Certain surrounding conditions are necessary to bacteria, and any marked change in them will inhibit the growth or totally destroy it.

Mechanical Conditions.—A slight shaking of a liquid culture seems to help the development of bacteria, while a more violent and long-continued agitation destroys them.

Physical Conditions.—*Electrical currents* destroy the growth, probably by the action of certain products of the electrolysis and not by direct action.

Light.—Diffused daylight inhibits the growth of bacteria: sunlight and, to a less extent, electric light destroy them. This is probably due to oxidation.

Heat.—A certain temperature is necessary, the degree varying with the species of microbe. Most of the water bacteria and saprophytes grow between 0° and 30° C. (32° and 86° F.), the optimum being 15° to 20° C. (59°–68° F.) (psychophilic). The pathogenic flourish between 10° and 45° C. (50° and 113° F.), best at the body temperature, 37° C. (98.6° F.) (mesophilic). There are some that develop well at 40° to 70° C. (104°–158° F.) (thermophilic). Above these limits the members of the several groups are killed, and each bacterium has its own thermic death-point. That of most of the pathogenic varieties lies between 50° and 60° C. (122° and 140° F.). Below the lower limit, down to the degree at which any multiplication will occur, the growth is inhibited only. Temperatures below zero destroy only the most feeble of parasites. Very low temperatures (–250° C.; –418° F.) have been used without preventing the future development of the microbe.

Spores are extremely resistant to higher temperatures. While no bacterium can live after exposure to 100° C. (212° F.), the spores of some of the earth microbes are killed only after exposure for an hour to steam heated to 115° C. (239° F.).

Chemical Conditions.—The essential substances for the growth of bacteria are water, carbon, nitrogen and oxygen, and certain salts. For the carbon, they require already prepared carbon compounds, as the sugars, glucose, saccharose, lactose, etc., mannite, glycerin—in fact, most of such as are soluble in water. Most of the proteins and many simpler substances, even such as ammonium carbonate, furnish the nitrogen. Free oxygen is necessary for many microbes. Those for which this is absolutely required are termed “obligate aërobic.” Facultative aërobic are those that grow best in the presence of oxygen, but may develop in its absence. Anaërobic microbes are those that grow best without atmospheric oxygen and are also obligate and facultative. They obtain it as they need it by reducing oxygen-containing materials in the culture-medium. It has been found possible to produce races which, although naturally obligate anaërobic, develop also in an atmosphere of oxygen.

FUNCTIONS AND PRODUCTS OF BACTERIA

The study of the substances that result from the action of the life of bacteria and the changes that they produce in their various media of growth is really a branch of organic chemistry. The function of bacteria is essentially a destructive one. They split up the higher nitrogenous and non-nitrogenous compounds into simpler substances.

The various substances that are found in cultures of bacterial growth comprise: (1) the components of the bacterial cell proper, as the proteins; (2) the secretions of the cell, as the ferments and toxins; and (3) substances that are the result of the action of microbes upon the medium of growth. The toxic substances in bacterial cultures may be classed as (*a*) intracellular and (*b*) extracellular, according as they are contained within the bacterial cell or are made from or excreted into the culture-medium. The extracellular substances may be purely products of bacterial secretion which have been separated from the cell, or they may be decomposition products derived from the culture-medium.

The bacterial **proteins** may produce suppuration (*pyogenic*) or fever (*pyrogenic*), or they may be the cause of an inflammatory process (*phlogogenic*). These substances are comparatively resistant to heat and are thus sharply distinguished from the ferments and toxins. The best-known examples are mallein, derived from the bacillus of glanders, and tuberculin, from that of tuberculosis. These are pyrogenic when injected into animals suffering respectively from glanders or tuberculosis, but have no, or at least very slight, effect upon healthy subjects. Other proteins are shown to have similar effects on tuberculous animals, but not in the minimal doses which suffice when tuberculin is used.

Vaughan and his associates claim that the protein of bacteria is divisible into a highly toxic non-specific portion, and a non-toxic fraction specific for each kind of organism. Upon this result and his further experimentation he has elaborated a theory of infection to be discussed later. The endotoxins are certainly closely bound with the bacterial proteins, but their exact seat is not known.

The second group of products includes the ferments and possibly the toxins.

Ferments.—A ferment is a complex body about which we know but little except the effects that it produces. By its presence, and probably without entering into intimate chemical combination, it possesses the power of breaking up more highly organized nitrogenous and non-nitrogenous compounds into simple and more diffusible molecules. They are termed *enzymes* or *unformed ferments* in contradistinction to the bacteria themselves, which are called *formed* or *living ferments*. That the action of ferments is not due directly to the microbe is shown by the facts that bactericidal substances, such as phenol (5 per cent.), chloroform, ether, etc., have no effect on them, and that cultures freed from bacteria by filtration still possess fermentative power. The action of ferments is termed *fermentation*, but this term

is more especially limited to the effect of certain ferments upon non-nitrogenous compounds, particularly the carbohydrates. The result of fermentation upon nitrogenous material is called *putrefaction*, which generally occurs with, though often without, the formation of odorous gases and other substances. The intracellular origin of certain ferments has been demonstrated by their experimental separation from the bacteria when placed under high pressures. The resulting bacteria-free liquid possesses the same fermenting qualities as the culture itself.

The ferments, like toxins, are of unknown composition, are highly destructible by chemical agents and heat, cause effects out of all proportion to their bulk or amount, and are frequently mechanically precipitated with various indifferent bodies. When injected into animals both are capable of exciting the formation of antibodies (anti-ferments and antitoxins).

Bacteria, as animal cells, have autolytic ferments. In this self-solution certain substances are freed that may be of importance in immunity reactions—endotoxins and aggrassin. The exact relation of bacterial digestion products, whether autolytic or by the agency of blood-serum or tissue fluids, is not exactly known. The demonstrable enzymes of bacteria have little to do with the specific infection caused by the growth aside from the softening of exudates and the like. This example is given to show also that one of the most important enzymes of bacteria is proteolytic in action.

The principal bacterial ferments are:

Proteolytic Ferments.—These transform albumins into more soluble and diffusible substances. One form very often met with is that which liquefies gelatin. This acts in an alkaline medium, and is, therefore, akin to the animal ferment trypsin. This liquefaction of the gelatin affords a means of distinguishing many species of microbes.

Diastatic Ferments.—These transform the starches into sugars, and are found in many bacterial cultures, as of *Bacterium mallei*, *B. pneumoniae*, etc.

Inverting Ferments.—These change the non-fermentisable sugars into those that undergo direct fermentation. Such ferments are found, for instance, in cultures of *Spirillum cholerae* and *S. metschnikovii*.

Coagulating Ferment.—One of the means of differentiation of bacteria is the coagulation of milk used as a culture-medium for the bacteria under observation. This coagulation is due not to acidity produced in the medium, but to the action of a ferment.

Some varieties of microbes produce a ferment that has the power of dissolving this coagulum when formed (casease); and still others produce both ferments—the coagulating and the dissolving.

Hydrolytic ferments are exemplified by such as break up urea into ammonium carbonate and hippuric acid into glycolic and benzoic acid.

Fat-splitting ferments split the fats into glycerin and the fatty acids.

Oxidizing and nitrifying ferments are other less important forms.

Effects of Ferments.—The single or combined action of these various ferments causes certain special kinds of fermentation distinguished by the principal substance produced. Alcoholic, lactic acid, and butyric acid fermentation of the sugars, acetic acid fermentation of alcohol (*Bacillus acidi lactici*, *B. butyricus*, *B. acidi butyrici*, etc.); cellulose fermentation with the production of carbonic acid gas and ammonia; nitrification, in which oxidation of ammonium leads to production of nitrates (Winogradsky's nitrosomonas), and secondarily conversion of nitrates into nitrites (nitrobacter); mucoid fermentation of glucose and invert-sugar are examples.

Toxins.—The pathogenic bacteria produce certain toxic substances that are akin in action to the poisonous venom of certain serpents and other animals, and to certain poisonous principles of plants, as abrin and ricin, and are almost certainly of protein nature. These are of indefinitely determined character, and act deleteriously upon the host only after the lapse of a certain time—a period of incubation. They are considered the *specific toxins* of the several bacteria. According to some, these give all the reactions of albumin, and have been termed *toxalbumins* (Brieger). It is probable, however, that the toxalbumin is but an impure form of the true toxin, a combination of it and various substances derived from the medium of growth. Most recent investigators look upon the toxin as akin to the ferments. Roux and Yersin, in their monograph on the diphtheria bacillus, held this view and more recent investigators support the theory. The analogous pathological action of the toxins and ferments, their common origin, their destruction (oxidation) in the presence of light, their precipitation by alcohol, their precipitation from solutions by colloid bodies, their long and imperfect dialysis, all point to this. High temperatures affect both similarly, both being destroyed at from 60° to 100° C. (140°–212° F.). Chemical substances that have no effect (chloroform, ether, etc.) on the ferments are without action upon the toxins; and, vice versâ, those that destroy the ferments (formaldehyd) are also injurious to toxins. They are, curiously enough, digested by proteolytic ferments. Both may be swallowed with impunity, although they are pathogenic when injected subcutaneously or intraperitoneally. When the microbe is grown in some inorganic medium or in a non-albuminous one (as Uschinsky's solution), the toxic principle obtained corresponds in its chemical reactions to a ferment. Most important is the fact that extremely minute doses are effective. Ferments act without regard to the mass employed, and it would seem that toxins act in almost imponderable amounts. It has been estimated that 1/1000 gm. of tetanus toxin will kill a horse weighing 600 kg.—six hundred million times its weight; and that 1/1000 mg. of tuberculin causes a reaction in a diseased man weighing 60 kg.—sixty trillion times its weight. Finally, both act only after a definite period of incubation.

Considerable light has been thrown upon the nature of toxins by the recent investigations of Ehrlich and others who have followed him. These investigations have been mainly concerned with the

behavior of the toxin toward the antitoxin bodies. Ehrlich has found that the serum contains at least three distinct substances: the toxin proper, toxoid, and toxon. The toxin is the active poisonous element; but, aside from its toxic property, it has a distinct combining ability, so that it enters into combination with antitoxin. A given serum, however, will combine with a greater quantity of antitoxin than the toxic power of the serum would indicate. In other words, there are other combining bodies which have no toxic power, or less toxicity than the toxin. A serum as it grows older loses in toxic power without losing in combining power. This is due to the conversion of toxin into toxoid. The toxon has, similarly, the combining power for antitoxin, but is slightly toxic, being capable, in the case of diphtheritic serum, for example, of producing the postdiphtheritic paralyses. It is, however, not a derivative of the toxin, but results from a direct action of the bacterium, and is produced simultaneously with the toxin. The dissociation of combining power and toxic power is explained upon the assumption that each molecule of toxin contains a group of atoms specially adapted for combining with vulnerable cells or with antitoxin and a toxic group. To the former the name *haptophore group* and to the latter the term *toxophore group* has been given. The probable nature of these will be referred to in the discussion of Ehrlich's theory of immunity.

Fate of Toxins.—It is certain that there exist in various cells of the animal organism certain oxidizing ferments by which the toxin is destroyed. Not all of the toxin is thus oxidized. A part is eliminated unchanged through the kidneys in the urine and to some extent through the liver in the biliary secretion. Besides these there is still another method of defence of the organism against the action of toxin—the antitoxin (*q. v.*).

PRODUCTS IN CULTURE-MEDIUM.

The third group of poisons found in bacterial cultures are the products of decomposition of the culture-medium under the influence of the bacterial growth. This is the class of poisons called ptomains, protein degradation bodies, with their nitrogen in the amino form. They act as a direct poison and require no specific incubation period. They differ from toxins in the fact that their elaboration is more closely dependent on the character of the medium than is that of the former. The toxin of tetanus or diphtheria may be produced in various, even in non-albuminous, media, but the elaboration of certain ptomains and other decomposition products is more narrowly restricted to growth of certain organisms in appropriate media. The substances produced by bacteria from the culture-media and tissues are varied and numerous. Besides those produced by the various fermentative processes there are: the products of digestion of albumin, albumoses, peptone, etc.; the ptomains; nitrogenous substances, as leucin and tyrosin, methyl-, dimethyl-, ethyl-propylamins; organic fatty acids, formic, acetic, propionic,

butyric, margaric, lactic, etc.; certain aromatic compounds, as indol, phenol, kresol, skatol, mercaptan, hydrochinon, etc.; and finally, hydrogen, carbonic dioxid, hydrogen sulphid, ammonium, water, etc. All of these are more or less toxic and may contribute to the unfavorable action of bacteria, but are not the specific toxic agents that occasion the characteristic pathological effects of the various micro-organisms.

Chromogenesis.—Many bacteria form colors which give to the culture a characteristic appearance. The production of the pigment depends to some extent upon the constitution of the medium, and it is possible to produce cultures and even races of pigment-forming bacteria by the use of appropriate media. It has no importance in the pathological relations of the organisms.

Photogenesis.—The phenomenon of phosphorescence observed in decaying fish is due to the action of bacteria. This production of light is observed in many of the cholera group of vibriones.

THE LOCAL EFFECTS OF BACTERIA

These may be either (a) mechanical or (b) histological, the mechanical effects being least in importance. (a) Sometimes masses of micro-organisms more or less completely occlude small blood-vessels and occasion secondary changes in the tissues in this mechanical way. In other cases the obstruction is incomplete, but occasions thrombosis in the blood-vessels and various consequential disorders. (b) The histological changes occasioned by bacteria are *proliferative* and *destructive*, among the latter being various degenerations and necrosis. The proliferative changes may be non-specific or specific—that is, there may be simply proliferation such as occurs from any irritation; or there may be special forms of proliferation more or less characteristic of the individual micro-organism in extent, distribution, and nature. This is seen in the peculiar lesions of tuberculosis, glanders, rhinoscleroma, etc. The cellular degenerations and necroses occur coincidentally or subsequent to the proliferative changes. On the contrary, in many cases the first effects of bacterial invasion seem to be degeneration or necrosis of the tissues immediately around the organisms.

EFFECT OF TOXIC PRODUCTS OF BACTERIA

This section of the subject is devoted to a consideration of the *modus operandi* of the foregoing bacterial products upon the body. The general principles apply to protozoan and metazoan parasites, but we deal here chiefly with bacteria. The action of all the animal parasites is not understood, and comment upon them will be reserved for the appropriate chapter.

Infection is the successful invasion of the tissues by bacteria and the evidences of their presence. *Infestation* is the term applied to the presence and action of animal parasites within the body.

The sources of infection (here and throughout this chapter we use

the term very broadly) are polluted objects—food, water, and insects. The action of each will be described when discussing the diseases to which they apply. This is the principal subject of hygiene and should be studied in works devoted to it.

It must not be forgotten that bacteria, even some pathogenic forms, are constantly present upon and within the human body. They are held in abeyance or destroyed by the primary defenses—the skin and mucous membranes. Should a lowering of these defenses or a great increase in the invasive powers of the bacteria occur, infection follows. The character of the infection depends somewhat upon the portal of entry or so-called infection atrium. Typhoid bacilli will not produce typhoid fever if rubbed upon the skin, but may if swallowed. Pus cocci may cause furunculosis if rubbed upon the skin, but will not if swallowed.

All openings to the body present possible infection-atria, and pre-existing disease of any part lowers the resisting powers of that part in particular and possibly of other parts. The most important infection-atria are the respiratory and alimentary tracts. Bacteria are inhaled or swallowed and lodge upon the mucous membranes. As has been said, these membranes are part of the primary defenses, but it has been shown that bacteria may pass them without leaving a trace. The invaders are met then by the resistance of the lymphatic system in which they are carried through the lymph-channels, or by the antibacterial power of the blood.

Pathogenicity is the power of the germ to produce disease. This does not always run parallel with virulence, as will be seen in the sub-acute infections. The power of the germs to resist the bodily defenses and, by their extra- or intracellular poisons, to produce a pathological effect, is their virulence. Ehrlich explains virulence by the statement that a bacterium is virulent to the extent that it has haptophorous or binding receptors to bind and sidetrack the defensive receptors of the body tissues. (See pp. 262, 263, and Immunity.)

An attractive theory has been suggested by Bail to explain the unusual virulence of micro-organisms under certain circumstances. It was found by Koch that intraperitoneal inoculation with fresh cultures of tubercle bacilli causes a rapid destruction of tuberculous animals. Bail found that if tubercle bacilli and sterilized tuberculous exudate were injected into healthy animals, sudden death resulted. Neither the sterile exudate nor the tubercle bacilli alone had such an effect. He, therefore, assumed that something in the exudate increases the virulence of the micro-organisms and gave the name "aggressin" to the hypothetical substance. The exudate found in the peritoneal cavity in these cases was found to consist solely of lymphocytes, and Bail suggests that the aggressin acts by paralyzing the polymorphonuclear leukocytes and thus prevents phagocytosis. The lymphocytic character of tuberculous exudates is explained by the presence of the aggressin in the tuberculous animal or man, and the consequent prevention of migration of polymorphonuclear leukocytes. Similar phenomena have been found

in cases of other micro-organisms. Anti-aggressins have been produced by repeated inoculation of animals with exudates containing the aggressins.

Some bacteria or their toxins have a predilection for certain tissues, as, for example, tetanotoxin for the nervous system. This and other phases of virulence will be considered under Immunity.

The probability of a successful infection varies directly with the number of organisms introduced, the virulence of the invaders, and with the resistance offered by the individual.

Intoxication and Infection.—In one class of diseases the infecting microbe remains localized at the point of inoculation, and is never or only exceptionally found in the fluids of the body, the general symptoms of the disease being due to absorption of the toxic products. In such cases the general symptoms of the disease are true *intoxications*. In other cases the microbe is found circulating in the blood throughout the body and finds lodgment in most of the organs. These are called *infections* in the strict sense. Tetanus is the type of the first class; anthrax, of the second. There is, however, no distinct line to be drawn, for the symptoms of all infections are doubtless due to toxins or other toxic products, whether produced locally at the point of implantation of the organism or throughout the body when it is disseminated. The distinction between intoxication and infection depends upon the method of toxin production.

The intoxications form a small class, of which diphtheria, tetanus, and botulism are the only practically important members. These diseases are due to extracellular poisons, commonly called toxins, which are made from the medium upon which the bacteria are living. For example, diphtheria bacilli growing on the pharynx pervert the normal bodily protoplasm to a toxic form. The toxin is negative, or at least antichemotactic (see Inflammation), and thus prevents the phagocytic action of the leukocytes; while most other bacterial products and the bacterial proteins are positively chemotactic.

The second class, the infections, is much larger. While it is possible that a modicum of extracellular poison is formed by microbes causing infection, it is certain that by far the greater amount is not available until the bacterial body is digested and the protoplasm liberated (endotoxin). The lysis of the germs may be focal or in the circulation, in either case due to the bacteriolytic power of the blood or to phagocytosis. Under Immunity and Allergie theories of the pathological action of these toxins will be discussed.

A virulent microbe is one that invades the animal body and there produces its more or less powerful toxin; an avirulent one produces but little, if any, toxin, and is destroyed by bacteriolytic substances and by phagocytosis, either with or without suppuration. The number of organisms, as well as the virulence, is important in determining the character of the effects.

Sapremia, Septicemia, and Pyemia.—From local suppurative foci, or necrotic areas due to saprophytic or non-virulent germs, toxic

products may be absorbed into the general circulation, and a condition known as *sapremia* results. The infecting bacterium itself may invade the blood-current without giving rise to any secondary lesions. This is termed *septicemia*. When, however, the microbe is carried to various parts of the body and there gives rise to secondary suppuration, the condition is called *pyemia*. *Bacteremia* is a term that may be used to indicate merely the circulation of bacteria in the blood without implying any clinical condition.

Infections may also be divided into *fulminating*, *acute*, *chronic*, and Adami's *subinfection*.

Fulminating infections are sudden overwhelming attacks by bacteria, in which all bodily defenses are destroyed and death results before new defenses can be raised.

Acute infections are those manifested by a short clinical course of more or less definite type and are the evidences of a brief depression of bodily defenses. They tend to be self-limited.

Chronic infection is the expression of struggle between the disease agent and bodily defenses over a long period and without definite stages. Tuberculosis is typical of such a disease.

Between this and the second form there is another, called variously subacute and chronic remittent. This may be a continuation of an acute condition or arise insidiously and cryptogenetically. The cases have constantly some evidences of infection, but are subject to remissions, acute in form, followed by disappearance of the more evident signs of infection when the exacerbation has passed. In cases studied by us there is persistent bacteremia. The cause seems to lie in a condition of balance between the bodily defenses and the bacterial offenses. Sometimes we have found that the failure of defense is on the part of the leukocyte; at others, on the part of the serum. The bacteria in these cases are in a condition known as "fast" or "fixed." We can only state that they seem to have immunized themselves in some way against the bodily defenses, and in so doing do not give rise to new defenses or antibodies. The bacteria may be considered as possessing a fairly well-marked pathogenicity, but a low virulence.

Subinfection, according to Adami, is a condition of repeated infection from the bowel or respiratory tract due to congestion or mild inflammation. These changes enable bacteria or their products to pass to the lymph or parenchymatous organs, where they are destroyed, their remains being found as amorphous granules resembling, but distinguishable from, pigment. The effect is that of continued or repeated irritation, and Adami believes they are factors in the production of cirrhosis and anemias. The focal infections of some writers belong in the subinfections.

Mixed Infections.—This is a state in which the effect of one agent is superimposed upon another, with usually an intensification of the symptoms or a rendering of them slightly atypical.

IMMUNITY¹

Definition.—In the present state of our knowledge of the condition of immunity it is most difficult to give a precise definition of this term. It denotes that condition of an organism which enables it to resist the attacks of bacteria and their toxic products. In one sense it is the reverse of susceptibility. An animal that is not susceptible to an infection is said to be immune, and the term “immunization” is applied to the process by which an animal becomes thus refractory.

Varieties.—Two principal forms of immunity, with a number of subdivisions, are recognized: (a) Natural immunity; (b) Acquired immunity.

(a) **Natural immunity** is the power of resistance to certain bacteria and toxins manifested by races or classes of men and animals, or even by certain individuals. It is always or nearly always an inheritance from immune ancestors, and can readily be accounted for on the principles of heredity. We may distinguish:

1. **Natural Bacterial Immunity.**—In this case the resistance is offered to some specific *bacterium*. Thus, none of the lower animals is susceptible to naturally acquired syphilis, measles, or leprosy; man is insusceptible to rinderpest; dogs and Algerian sheep, to anthrax; chickens, to tetanus; and in epidemics of various kinds some individuals regularly escape. This bacterial immunity² is only exceptionally *absolute*; usually it is merely *relative*, the susceptibility or insusceptibility varying with the environment or individual conditions.

2. **Natural Toxin Immunity.**—Just as the hog is naturally resistant to snake-venom, so certain animals are immune to certain bacterial toxins. Rats are resistant to diphtheria toxin; chickens, to tetanus toxin, etc.

(b) **Acquired Immunity.**—This may be *naturally acquired*, as when an animal has passed through an infectious disease; or *artificially acquired*, when an animal or man has been inoculated with bacteria or bacterial products. We may again distinguish two subvarieties, as in the case of natural immunity:

1. **Acquired Bacterial Immunity.**—In this form the animal or man has been rendered immune by previous naturally acquired disease, or by inoculation with the specific organisms that have been first reduced

¹ Certain definitions and synonyms must be understood to read properly this and other articles on immunity:

Antigen, or exciting substance, is the bacterium cell or substance used for immunizing to produce *antibodies*; these, then, are substances formed against antigens.

Toxin, ferments are the soluble products of disease agents.

Toxophore, the poisonous or intoxicating fraction of an antigen.

Haplophore, the binding fraction of antibody or antigen.

Complement, cytase, alexin, the normal thermolabile antiserum in blood-serum.

Zymophore, the toxic radical in agglutinins and precipitins.

Cytophile fraction of antibody combines with cells.

Complementophile fraction of antibody combines with complement.

Immune body, amboceptor, intermediate body, fixateur, substance sensibilisatrice, preparateur, copula, and desmon are synonyms for the thermostable body raised against antigens.

² The various immunities of animals are not always absolute under experimental conditions. It is possible to give monkeys and, probably, rabbits syphilis, but they do not have syphilis as an endemic among them; it is not natural to lower animals.

in virulence or killed by heating and other means. Acquired bacterial immunity does not follow all infections. In the case of gonorrhea, for example, it is wanting; and in erysipelas there seems to be increased susceptibility; but in most of the infections immunity is produced. It is of variable duration, sometimes lasting throughout life, sometimes only brief periods of time.

2. *Acquired Toxin Immunity*.—In this form the immunity is produced by the injection into animals of the toxins from bacterial cultures, or by injection in men or animals of serum of animals that have been rendered naturally or artificially immune.

The terms “active” and “passive” are used in connection with types of immunity to designate the active or passive part taken by animals or men in the acquirement of the immunity.

Active Acquired Immunity.—This term is applied when artificial bacterial immunity or toxin immunity has been produced by inoculation with living or dead bacteria or by injection of filtrates of cultures, because in these cases there is *active production* of the immunizing substances in the body of the experimental animal.

Passive Acquired Immunity.—This term is applied to the protection afforded by injections of serum of immune animals, because in this case the process is passive as far as the recipient of the antitoxic injection is concerned. Active immunity is relatively much more lasting than passive.

In many cases immunity asserts itself against both the infecting microbe and its specific toxin, as in the rat with regard to the diphtheria bacillus and its toxin; but more often an animal is resistant to the infection, though susceptible to the toxin. An example of this is the action of the guinea-pig toward tetanus (Vaillard). The reverse may be true, and we see an injection of tuberculin without effect upon a healthy animal that is very susceptible to tuberculous infection. Most commonly natural immunity exists toward the infecting microbe and not its toxin.

Theories of Immunity.—All the phenomena of immunity have not been satisfactorily explained, but the subject is at least much clearer than formerly.

Bacterial Immunity.—*Alexin Theory*.—The blood-plasma and fluids of a naturally immune animal are capable of destroying the bacteria toward which the animal is immune. That the destructive agent is contained in the blood itself is shown by the fact that the defibrinated blood and pericardial effusions of dogs and rabbits destroy anthrax bacilli outside the body. This bactericidal action is not, however, specific nor confined to serum from animals naturally immune to certain infections. On the contrary, the destructive action is manifested toward all micro-organisms in varying degrees, and the serum of man or animals always manifests bactericidal power, though not always decidedly. This bactericidal action was attributed by Buchner to certain albuminous bodies which he termed “alexins.” These are unstable substances resembling ferments in action and easily destroyed by heating

the serum to from 55° to 60° C. (131°–140° F.). It has been recently shown that the protection in bacterial immunity is not afforded by a single body or alexin, but by two distinct substances, each of which is necessary. (See Ehrlich's Side-chain Theory.)

Phagocytosis.—Metschnikoff proposed the very attractive theory of phagocytosis. He has, however, modified his older views because of new experimental work along the lines laid down by Ehrlich. He now maintains that phagocytosis is the principal factor in immunity and that soluble immune bodies in the plasma are derived from leukocytes. Even extracellular digestion of bacteria is due to substances from leukocytes. The infecting microbes are taken up by certain cells of the organism and are destroyed by intracellular digestion, or are dissolved by ferment-like bodies derived from phagocytes when they break (phagolysis). These cells—*phagocytes*—are of two kinds: the microphages, including the polymorphonuclear leukocytes; and the macrophages, including mononuclear leukocytes, the vascular endothelial cells, cells of the bone-marrow and spleen, certain connective-tissue cells and Kupfer's cells, and even those of the nerve and muscle tissue. The microphages are mainly concerned in the absorption and destruction of bacteria; the macrophages, in the destruction of cells, portions of dead tissues, and the like. After injection of a culture into the subcutaneous tissue of an animal naturally or artificially immune, he noticed that the bacteria were all taken up by the leukocytes. That these microbes were still living and virulent, and were not taken up as mere dead matter, Metschnikoff regards as fully established. One proof he cites is the fact that an exudate containing no free bacteria, but all intracellular, is capable of producing cultures on artificial media and causing infection in susceptible animals. The ferment freed by disintegration of phagocytes Metschnikoff called "cytase."

Certain important features of Metschnikoff's theory and results must be emphasized. Increase of resistance to bacteria is usually associated with an increased phagocytic power, but not always, and occasionally an infection, during which the blood and leukocytes possess high phagocytic power, results fatally. In some infections an immunity results, although we cannot perceive any change in the leukocytes. It has not been proved that antibodies arise from phagocytes. The cellular theory of Metschnikoff is not incompatible with the humoral or side-chain theory of Ehrlich, but merely explains certain phases of immunity reactions. The phagocytes are, undoubtedly, very important bodily defenses. One of the most difficult phases to explain in terms of this theory is the mechanism of the ill-understood increase in virulence. Organisms are resistant to phagocytosis directly as virulence changes, yet it is possible to get an immunity to a virulent organism without phagocytic action.

Bacteriolytic Theory.—Pfeiffer opposed to Metschnikoff's theory the experiment of injecting cholera vibriones into the peritoneum of artificially immunized guinea-pigs. He observed a complete destruction of the microbe by the peritoneal fluid—an agglutination into

masses and a gradual degeneration. There were few, if any, leukocytes present, and he, therefore, claimed that such destruction was entirely extracellular and humoral in character. This property of destroying or dissolving bacteria has been termed the "lytic" action of serum. However, if a preliminary injection of some substance that determines a local leukocytosis is made, there may occur, instead of the reaction of Pfeiffer, a true phagocytosis. Metschnikoff interprets Pfeiffer's phenomenon as the result of a dissolution of the leukocytes by bacterial action, and solution in the peritoneal fluid of the bacteriolytic substances.

While an important part must be admitted to phagocytes in the ultimate destruction of bacteria, bacteriolysis may occur independently of phagocytes.

The bacteriolytic substance has been found to operate outside of the body, though not so actively as in the peritoneal cavity. When it has been partly destroyed by long standing or heat, the addition of a small quantity of normal serum from the same animal species restores the bacteriolytic power. (These phenomena will be again referred to in the discussion of Ehrlich's Theory.) The sources of the bacteriolytic substances are the spleen, bone-marrow, lymphatic glands, thymus gland, and doubtless other organs as well. It is probable that the source differs in different infections.

Bacteriolysins differ from Buchner's alexin in being specific in action, and, therefore, operative only in the case of bacteria to which the animal has been immunized. The bacteriolysins are closely related to, if not identical with, hemolysins, substances occurring in the plasma under certain conditions and capable of destroying red blood-corpuscles. (See Ehrlich's Theory.)

Opsonins.—Wright and others have demonstrated in the serum of animals certain thermolabile bodies which, acting upon bacteria, sensitize them for phagocytosis. These substances, which have been termed *opsonins*, are analogous in constitution to toxins in having a haptophore group by which they attach themselves to the bacteria, and an opsoniferous group, which resembles the complements, and, acting like a ferment, completes the sensitization of the bacterium.

The natural serum opsonin is thermolabile, but that arising in immune animals is decidedly more resistant to heat. It is believed by many that native opsonin is akin to complement or alexin, while that appearing after active immunization is in the nature of a specific antibody and, therefore, a new development. Such antibodies are certainly specific for the type of organism, if not individually specific. There has been a tendency to minimize the effect of the leukocytes by those engaged in opsonin work. The phagocytes are not inactive or neutral, leaving all the work to the serum opsonin. Whether or not we accept the theory that all such free serum bodies come from the leukocytes, these cells are undoubtedly responsible for certain increase or decrease of phagocytic power, as we have found in certain subacute infections (see p. 254). Leukocytes and their extracts have a slight bactericidal effect *in vitro*, as shown by Petterson. This may have some effect *in vivo*,

but such an action is not considerable. The substances extracted from leukocytes are called "endolysins" by Petterson.

The knowledge of opsonins and phagocytosis has led to the modern uses of dead bacteria or their products for increasing immunity. This process has been called vaccination because of its similarity in principle to the antismall-pox vaccine. In typhoid vaccination there may be no high tide of opsonin or other antibody value maintained for a great length of time, but after exposure to typhoid there seems to be a prompter and greater response in the vaccinated than in the unvaccinated person.

Bacterial Agglutination.—Investigations by Gruber, Durham, Widal, and others have shown that the serum of animals or men rendered immune (naturally or experimentally) to infection with the bacilli of typhoid fever, cholera, the *Bacillus coli*, etc., causes agglutination and flocculent precipitation of the respective bacteria from their bouillon cultures. Such reactions may be obtained with dead bacilli under certain conditions and even with inert matters held in suspension. (For further details see Typhoid Fever.) This phenomenon (*reaction of Gruber-Widal*) has been interpreted as representing the mode of defence of the body against infection, and the reaction has, therefore, been considered as one of immunity. The reaction, however, bears no relation to the severity of the infection or the degree of immunity. The serum may be highly agglutinative and yet have no immune properties. Some have thought that the agglutination is closely associated with bacteriolysis, perhaps as a preparatory step, but the two functions are certainly distinct.

Recent experiments seem to show that two substances are concerned in agglutination—an agglutinable and an agglutinating body. The latter appears to be albuminous or related to serum-globulin, as it is precipitated with the latter by magnesium sulphate. It is much more resistant to heat than alexin.

Ferment Theory.—A ferment theory has been offered in explanation of some of the phenomena of immunity, but it is of only restricted interest or importance. Certain bacteria, like pyocyaneus, typhoid, and cholera bacilli, are capable of elaborating ferment-like bodies that have been designated *pyocyanase*, *typhase*, and *cholerae*. These have some bacteriolytic power, and natural immunity has been explained by assuming the presence in the plasma of such ferments. The action of these ferments is not, however, specific, and their relations to other bacteriolytic bodies is still obscure.

Toxin Immunity.—The probable nature of toxins has been discussed on page 249. It is found in some cases that an animal is susceptible to the action of the toxin of a certain bacterium, though refractory to the bacterium itself, and the reverse may also occur. It is clear, therefore, that the resistance to bacteria and to toxins are distinct processes, though the two are in most instances associated in the same animal.

Natural Toxin Immunity.—Certain classes of animals exhibit natural toxin immunity just as we have seen natural bacterial immunity

existing in certain animals. The immunity of the hog to snake venom, of the chicken to tetanus toxin, of the rat to diphtheria toxin, and other examples might be cited. The explanation of this natural immunity is still uncertain. It is supposed that the immunity, which is an hereditary one, originally occurred in the ancestors as a result of the infection or intoxication in question. They then transmitted the immunity to their descendants. With the discovery of antitoxin (to be described below) it seemed likely that an explanation of natural toxin immunity had been discovered, but it was found that, in the case of the chicken and rat, not a trace of antitoxin is present in the blood, though these animals are highly immune to the toxins of tetanus and diphtheria respectively. It was also found that in these animals the introduction of the toxins, while producing no symptoms, rendered the serum highly toxic, and that, transferred to other animals, this serum produced the symptoms of the diseases named. The toxin evidently circulates in an unaltered state at least for some time, and the immunity is not due either to destruction of the toxin or to its rapid elimination; and as antitoxin is absent, it seems likely that the immunity rests upon an unreceptive quality in the cells of the body. Recent experiments have made it clear that toxins attach themselves closely to certain cells, as, for example, the nerve-cells in the case of tetanus; and it may easily be conceived that if these cells are not receptive, the toxin might circulate harmlessly in the serum. Experimental proof of this view will be cited later.

The term *antitoxin* is applied to a substance or substances in the serum of an animal that protect against the toxin of a specific disease.

Acquired Toxin Immunity.—This condition was first explained by Behring in a manner similar to the explanation at that time offered for natural toxin immunity—that is, he taught that the tissues of the body become accustomed to the toxin, a sort of Mithridatization. Later he recognized that the resistance is due to the presence of an antitoxin. This at first was regarded by many as an altered form of toxin, and among other experiments offered to prove this view was that of generating antitoxin *in vitro* by the action of either a continuous electrical current or a rapidly interrupted direct current. It is very likely, however, that the supposed antitoxin in this case was simply a toxin of lower virulence, and that its seemingly antitoxic character was really due to its capacity for developing immunity when injected into animals.

Behring first produced antitoxin of diphtheria, but since his investigations antitoxins of tetanus, snake-venom, and of various infectious poisons, mainly of laboratory interest, have been produced. The production of antitoxin is accomplished by treating an animal at first with small, and later with larger, doses of the toxin until the antitoxic quality is developed. As a matter of practical procedure in some cases (*e. g.*, diphtheria) cultures that have been sterilized by heat or cultures containing bacteria of low virulence are frequently used in the early injections, and later, when a certain degree of immunity has been pro-

duced, the animal is inoculated with virulent cultures until the antitoxin reaches a maximum. When toxin of sufficient strength can be obtained, the antitoxin can be most surely prepared by using the toxin alone.

Occasionally antitoxin is found in the normal animal or in man without previous occurrence of the infection under consideration; thus, in a notable proportion of normal horses, diphtheria antitoxin is found in the blood, and the same is true of children and of adult human beings. In these latter, of course, the possibility of a slight attack of the disease occurring in early life and having been overlooked must be considered. In animals, such as horses, in which the disease does not occur spontaneously, this explanation does not hold. In the light of recent knowledge it seems probable that antitoxin may be produced by the cells under stimulation other than that of the specific toxin, and while antitoxins are specific to a very large degree, so that that of diphtheria protects only against the diphtheria poison and that of tetanus only against the tetanus poison, this specificity is not absolute. It is known that diphtheria toxin protects against abrin-poisoning, and the antitoxin of abrin protects against abrin- and ricin-poisoning, while the tetanus antitoxin is partially preventive against snake-venom. In other words, the blood has some natural antitoxic power which is increased as a non-specific body at the same time that specific antitoxins are being formed. Moreover, there are certain common constituents in various antitoxins that may possess a generic antitoxic power.

Several years ago Theobald Smith showed that a nearly neutralized mixture of toxin and antitoxin produced a more lasting immunity to toxin than simple toxin. This has lately been put to practical use by Behring and his students. The loose chemical union of the two, formed *in vitro*, is broken up in part by the body, which then proceeds to form its own antitoxin. A too rapid effect of freed toxin is held in check by the accompanying antitoxin.

Action of Antitoxin.—It was first thought by Behring that the toxin and antitoxin enter into a chemical combination which completely destroys the identity of the two substances. This was disproved by the discovery that a mixture of snake toxin and its antitoxin, which ordinarily has no effect when injected into an animal, becomes highly toxic when heated to 70° C. (158° F.). It is known that the antitoxin is destroyed at this temperature, while the toxin is not. It is very probable that the toxin and antitoxin enter into a form of loose chemical combination without losing their identity, just as hydrochloric acid enters into loose combination with albumin in gastric digestion.

The Chemical Nature of Antitoxin.—But little is known regarding the antitoxins excepting that they are relatively resistant to heat and other external agencies. Thus, the tetanus antitoxin bears a temperature of up to 70° C. (158° F.), as well as the action of sunlight, and even putrefaction, without being destroyed. It seems likely that the antitoxins are albuminous bodies or that they are closely associated with such bodies.

Transmission of Antitoxin.—The hereditary transmission of anti-

toxin has been studied, and it has been found that transmission takes place from the mother to the offspring through the fetal circulation or, after birth, through milk. There is no transmission from an immune male parent to the offspring. In experimental work the transmission of immune substance could not be traced as far as the second generation.

Elimination.—Antitoxin is probably eliminated through all the secretory organs. It has been found in the urine and to a large extent in the milk. Brieger and Ehrlich obtained a quite concentrated form of antitoxin by precipitation of the globulin by ammonium sulphate and purification by dialysis. As in the case of toxins, the whole of the antitoxin seems to be carried down by the precipitated globulin.

All the phenomena of immunity have been explained by Ehrlich in a very comprehensive theory called the *side-chain theory*. The applications of this to toxin immunity will be first considered for the sake of simplicity.

Ehrlich's Side-chain Theory.—*Toxin Immunity.*—This theory explains the facts regarding the action of toxins and the formation of antitoxins better than any that has been suggested. It is based upon the hypothesis that bacterial toxins, like assimilated foodstuffs, enter into chemical combination with the cells of the body. In this respect toxins differ from ordinary poisons which do not enter into such combination, and this may explain the failure of all experiments at production of antitoxins for such poisons. Some non-bacterial poisons, such as snake-venom, abrin, ricin, etc., resemble toxins in combining with the cells, and it is notable that in the case of these poisons antitoxins have been produced. The combination between a toxin and a cell is effected by atom groups or radicals (to borrow terms from organic chemistry), the group of the cell entering into combination with the group of the toxin. It is assumed that the body-cell is like a complex chemical substance with unsatisfied bonds, to which is added the power to combine with substances having affinity for it through these bonds, and to cast them off after this new combination is effected. These groups which effect the junction of the cell and the toxin are termed *haptophore groups*. In addition to its haptophore group, the toxin molecule contains a *toxophore group* which carries the toxic capacities, but the toxophore group cannot operate upon a cell until the toxin has been anchored to the cell by the junction of the haptophore groups (Fig. 96). When a toxin is introduced into the body, it finds cells with haptophore groups having affinity for its own haptophore group. These haptophore groups of the cells, from their receptive function, are called *receptors*, and they are specific in so far as the receptors of certain cells will combine with the haptophore groups for which they have affinity and with no others. In this way it may happen that a highly toxic body may circulate harmlessly in the body, as there are no receptors for which it has affinity. (This matter was referred to in the paragraph on Natural Toxin Immunity.)

When the receptors of the cells are utilized by combination with the haptophores of the toxin they may be regarded as neutralized or practi-

cally destroyed, and the cell has suffered a "defect" which must be replaced by regenerative processes. This usually follows promptly, according to the well-known theory of Weigert that destruction is followed by regeneration. In accordance with the same theory this regeneration often more than replaces the loss, so that in the case under discussion there is an overproduction of receptors in the cell, and some of these are extruded from the cell into the blood-plasma. The actual extrusion or separation of the haptophore groups requires the stimulus of the toxophore group. The separated haptophore groups now free in the blood-plasma constitute the *antitoxin*, since they are now free and able to combine with the toxins before these can reach cells susceptible to the action of the toxophore group. The toxin thus combined with a liberated recep-

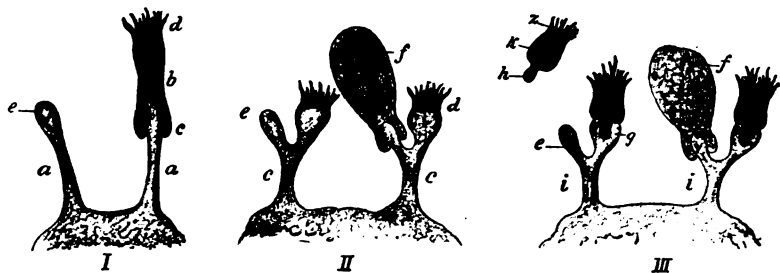


Fig. 96.—Receptors of three orders (Ehrlich).

Ehrlich has described receptors of three orders: 1. The receptor of the first order is a single combining group without any other function. On this account Ehrlich speaks of it as a uniceptor. In Fig. 96, I, such receptors are shown at *a*. On the right hand, the receptor has become united with a toxin molecule, *b*. The latter shows its haptophore group at *c*, and its toxophore group at *d*. It is the receptor of the first order that constitutes antitoxin when liberated from the parent cell. 2. Receptors of the second order (Fig. 96, II, *c*) have a haptophore group, *e*, and a symphore group, *d*. The latter is so named because of its ferment-like capacities. On the right hand is seen a molecule of nutrient matter, *f*, combined with the haptophore group of the receptor, in such position that the symphore group can act upon it. Having but one haptophore group, like the receptors of the first order, those of the second order also are included under the term of "uniceptors." The phenomena of agglutination and precipitation are probably occasioned by this second order of receptors. 3. Receptors of the third order (Fig. 96, III, *i*) carry two haptophore groups, *e* and *g*. One of these combines with a molecule or cell, *f*, for which the receptor has affinity, and the other combines with the haptophore group of the complement, *k*, which, when so combined, can act upon the molecule anchored to the other haptophore group. The complement has two groups—one, its haptophore, *h*, and the other, its zymotoxic group, *z*.

tor (antitoxin) is incapable of harm, as its own haptophore group is promptly joined to the antitoxin and cannot, therefore, become anchored to a vulnerable cell, which is the prerequisite for the operation of the toxophore group upon a cell. After antitoxin formation has begun, it may continue for some time, causing successive discharges of the antitoxic material into the blood-stream. This is shown by the continued presence of antitoxin in animals that have been bled so abundantly that practically all the original blood must have been withdrawn.

All the steps in this theory have been practically demonstrated. In the first place, it has been shown that the toxin enters into firm combination with the cell by mixing tetanus toxin and emulsions of

normal brain tissue. Under these circumstances a certain proportion, or all, of the toxin unites with the nerve-cells, and the mixture is found to be harmless when injected into animals. In the second place, it has been shown that the receptor *formation* results from the combination of the haptophore groups of the toxin and of the cell, and is independent of the toxophore group. This was demonstrated by producing increased susceptibility to the action of toxin in animals inoculated with toxoid (a body derived from toxin, but having no toxic qualities). The toxoid has the same combining capacity for receptors of the cells as has the toxin, but it simply lacks the toxophore groups, which somehow have disappeared or become altered. In the experiment just quoted there was no trace of *antitoxin* in the blood; hence the toxoid was capable of causing increased production of receptors *on the cells*, but not free in the blood as antitoxin. Other experiments show that the stimulus of the toxophore group is necessary to cause the *separation* of new-formed



Fig. 97.—I. Scheme showing cell with receptors (a). One receptor has been occupied by a toxin molecule (b). There has resulted an overproduction of receptors, and two of these (a') have become separated from the cell.

II. Scheme showing toxin molecules (b) attached to free receptors (a') in the blood. The toxin is thus prevented from attaching itself to the receptors (a) of the cell, and the toxophore group (d) is harmless.

receptors from the cell. In the third place, it has been shown that the antitoxin formation takes place in the fixed tissue cells, where the toxin finds suitable receptors, and not in the circulating blood itself, since antitoxin could be extracted with salt solutions from the blood-making organs of animals that had been treated with toxin, but had not yet any antitoxin in the blood. Of course, the period of time during which such an experiment could succeed must be a very brief one, but it has been accomplished.

Numerous experiments have shown that the antitoxin is not altered toxin, but a new production, as stated in this theory. The large amount of antitoxin produced by a small amount of toxin alone would suffice to disprove the theory of transformation.

Haptophore groups or receptors still in connection with the parent cell are not to be regarded as antitoxin; rather the contrary, for they serve to anchor the toxin to the cell where the toxophore group is in

position to injure the cell (Fig. 97). The experiment quoted above showed this, for the animal treated with toxoid developed increased vulnerability to toxin (because of the increased number of receptors) and had no trace of antitoxin in its blood. It is only haptophore groups that are free in the circulation, and therefore capable of fixing toxin and keeping it away from the cells that constitute antitoxin.

This antitoxin production Ehrlich ascribes to his *uniceptors* or *receptors of the first order*. It is the simple union of toxin haptophores and fixed or free cell receptors.

Bacterial Immunity.—(a) *Bacterial immunity as applied to agglutination and precipitation* is next in order. These processes are explained by Ehrlich's *receptor of the second order*. This assumes that the cell receptor has two parts, one to combine with the haptophore of the bacterium or other body, the other a zymophoric part, to act upon the toxophoric part of the bacterium (see Fig. 96).

These processes—agglutination and precipitation—are not actively concerned in the phenomena of immunity, but may be referred to in this place on account of their illustrating the applications of the side-chain theory.

Agglutination.—Bacterial agglutination (Pfeiffer-Gruber-Durham phenomenon) is explained by Ehrlich's theory somewhat in the same way as bacteriolysis and hemolysis. In the case of agglutination, however, there is but one agent—a liberated amboceptor having a haptophore group, which attaches itself to the bacterium, and a zymophore group, which plays a part similar to that of the complement in bacteriolysis (see Fig. 96, *II, d*). It differs from the complement, however, in that the zymophore group is an integral part of the amboceptor, and not a separate body, which attaches itself to the latter. A serum which has the property of agglutinating the bacteria of a certain disease (as *e. g.*, typhoid fever) contains liberated amboceptors that were set free by the cells of the body and that have the property of attaching themselves to the specific bacteria concerned in that disease. When so attached, their ferment-like group or zymophore group, which is the active agent, produces agglutination. The zymophore of the antibody is the agglutinating substance or agglutinin, while the corresponding fraction of the bacterium is the agglutinable body. This was mentioned on p. 259. (See also Typhoid Bacillus.) Agglutinins are also found in normal blood, although in but small quantity. They are thermostable, and resist drying of the serum.

Precipitin.—The phenomena of precipitation of various substances that have been introduced into an animal organism by the action of serum derived from the blood of such animals have been ascribed to specific "precipitins." Thus, when the blood of human beings is repeatedly introduced into the peritoneal cavity of rabbits, the rabbit-serum acquires the property of precipitating human blood. When the blood of several animals in succession is introduced into an animal of a different species from each of these, it is found that the precipitation is a specific process, since the specific power to precipitate the blood of each

of the species employed can be successively demonstrated. When albuminous liquids or such a complex mixture as milk is introduced into animals, the blood-serum of the animals acquires the property of precipitating the albumin used or the milk (casein). This and other experiments show the wide range of applicability of the principle of precipitation. Ehrlich explains the process of precipitation in the same way as that of agglutination, by the assumption that amboceptors carrying haptophore groups with an affinity for the precipitable body are set free in the serum, and that associated as an integral part of these amboceptors are zymophore groups capable of producing the phenomenon of precipitation or agglutination. The zymophore groups are destructible by heat, though the degree of heat is much higher than that required to destroy the complements concerned in bacterial destruction and hemolysis.

(b) *Bacterial Immunity as Applied to Bacteriolysis and Cytolysis.*—The application of Ehrlich's theory to the phenomena of bacterial immunity is quite as satisfactory as it is to the formation of antitoxins. When a bacterium is introduced into the body, the problem of the defence of the organism against the invading bacterium is much more complicated than that of the defence against a toxin, because the bacterium contains a variety of substances, such as its protein and various ferments, and may elaborate specific toxins in the culture-medium. In consequence, the defence of the animal organism against the bacterium is a complicated one, involving formation of antitoxin and other antagonistic bodies, including those which attack the bacterium itself in contradistinction to the products of the bacterium. The defense against the bacterium is the process that has been referred to previously in describing Pfeiffer's phenomena of bacteriolysis. This process, according to Ehrlich's investigations, is practically identical with that of hemolysis, or destruction of red corpuscles, which occurs when the blood of one animal is injected into another, or when certain hemolytic agents, like snake-venom, are introduced into the blood. As the study of hemolysis is practically much easier than that of bacteriolysis, the theory was elaborated on the bases of experiments in hemolysis, and two distinct substances or bodies are involved in the process. One of these Ehrlich formerly designated as the *intermediary body* in the case of hemolysis, or the *immune body* in the case of bacterial immunity; the second is a complementary body, and is designated the *complement*. The intermediary body, or immune body, is a product of cell activity under the influence of infectious, toxic, or other agencies, which is set free in the same manner as the haptophore group or receptor in the case of antitoxin formation. It has two haptophore groups—one having affinity for the complement, and therefore designated *complementophilic*; and the other having affinity for the bacterium, red corpuscle, or other cell, and therefore designated *cytophilic*. On account of this possession of two haptophore groups Ehrlich later designated the intermediary body by the term *amboceptor*. This is Ehrlich's *receptor of the third order*. It is a stable substance, not influenced by

moderate heat. The complement, on the other hand, is a ferment-like body, and is a constituent of normal blood-plasma. Its ferment-like character is evidenced by its ready destructibility by heat (55° or 56° C.; 131° or 132° F.). The origin of complement has been variously ascribed to leukocytes, lymph-glands, and liver. Without the complement the amboceptor is ineffective, and without the amboceptor the complement cannot affect the cells (bacteria, red blood-corpuscles, etc.). The cytophilic group of an amboceptor is more or less specific, so that, unless the receptors (haptophore groups) of the bacteria, red corpuscles, etc., are homologous with the cytophilic haptophore of the amboceptor, combination will not occur—in other words, the amboceptors are more or less specific and must be homologous with the receptive haptophores or receptors of the cells. There must, then, be a great many varieties of receptors—perhaps hundreds or thousands—in order to fix the equally numerous varieties of amboceptors, and the same is perhaps true of the complement. Various substances doubtless act as complements. Thus, in experiments on snake-venom, Kyes found that lecithin is the complement.

The bacteriolysin of Buchner, called by him *alexin*, is, according to recent views, a compound substance, one part being the amboceptor, the other the complement.

Explanation of Pfeiffer's Phenomenon.—The phenomenon of Pfeiffer's bacteriolysis may be explained in the following manner: When a bacterium, with a quantity of immune serum, is introduced into the peritoneal cavity of a *non-immunized* animal, amboceptors derived from the immune serum attach themselves to it. The complement present in the peritoneal fluid then becomes anchored to the complementophilic haptophore group of the amboceptor, and in this position is able to bring about the solution of the bacterium and its destruction. The phenomena of hemolysis may be explained in the same way: the amboceptor first attaches itself to the red corpuscle, and the complement (hemolysin) in turn attaches itself to the amboceptor.

The necessity for two bodies in the production of these phenomena has been thoroughly demonstrated. It is known that serum capable of producing Pfeiffer's phenomena *in vitro* loses this power when subjected for a certain length of time to heat or sunlight. A prompt restoration of the power follows the addition of small quantities of normal (unheated) serum of the same animal species. This proves that a ferment-like body (destroyed by heat) is a necessary factor, and that this ferment is present in the normal serum of the animal. The importance of the complement has been further demonstrated by the formation of anti-complements, which are capable of combining with it and thus stopping its action. When the anticomplement is withdrawn, the complement is again capable of operating. In a similar manner anti-amboceptors have been produced, and have sometimes been found in the blood of normal animals.

The following scheme represents graphically the relations of the amboceptor and complement to the cell and the possibilities of the

various antibodies, such as the anticomplement and anti-amboceptor (Fig. 98).

Cytolysin.—Injections of emulsions of various cells into animals have been found to generate destructive substances in the serum of the experimental animals. These destructive bodies are specific for the cells used in the experiment. Thus, spermatolysin, epitheliolysin, and hepatolysin are substances which will cause destruction of spermatozoa,

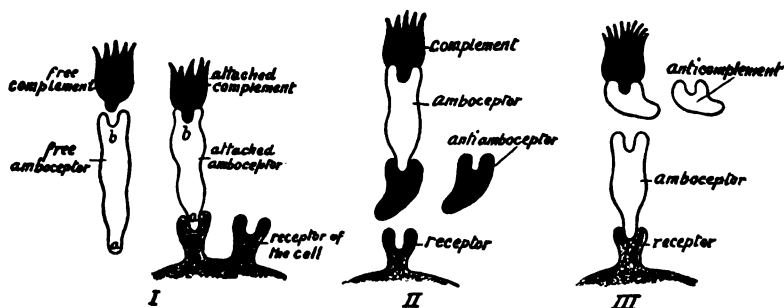


Fig. 98.—I. Diagram representing the amboceptor and complement free and attached to the cell by means of the appropriate receptor. II and III. Scheme showing (1) possible antibodies; (2) anti-amboceptor; (3) anticomplement; both of these have been demonstrated as possible antibodies. a, Cytophilic group; b, complementophilic group.

epithelia, and hepatic cells respectively. The phenomena involved in such cytolysis are closely allied with those of bacteriolysis and hemolysis.

The following tables (modified from Müller) will show in a condensed form the varieties of immunity detailed in the foregoing paragraphs:

Antitoxic Immunity

I. Cellular.

A. Lack of appropriate receptors.

- (a) Congenital.
- (b) Acquired (loss of the receptors).

B. Lack of susceptibility to the toxophore group of the toxin.

- (a) Congenital.
- (b) Acquired (?).

C. Attachment of the toxin to insusceptible tissues.

- (a) Congenital.
- (b) Acquired (development of new receptors in insusceptible tissues).

II. Hematogenic.

A. Active.

- (a) Manifest form (abundance of antitoxin in the blood).
- (b) Latent form (no antitoxin present, but capacity for making it quickly and abundantly).

B. Passive.

Antitoxin is introduced:

- (a) Through the placenta to the fetus.
- (b) Through milk to the nursling.
- (c) By direct injection.

Antibacterial Immunity

I. Natural (congenital).

- (a) The animal organism is an unsuitable medium for the growth of the bacterium.
- (b) The organisms are destroyed at the point of infection by amboceptors and complements (bacteriolysis).
- (c) Amboceptors present, but no complements.
The latter are supplied by—
 - 1. Increased supply of tissue fluids.
 - 2. Advent of wandering cells.
- (d) Complement present, but no amboceptors.
The latter are supplied—
 - 1. Locally.
 - 2. By the lymphoid blood-making organs.
- (e) Phagocytosis and intraphagocytic bacteriolysis.

II. Artificially increased, but not specific (pseudo-immunity). Injection of irritating substances which cause local accumulation of phagocytes and bacteriolysins.

III. Naturally acquired specific immunity.

IV. Artificially acquired specific immunity.

- (a) Active immunity.
 - 1. Abundant presence of specific amboceptors in the blood and tissue fluids.
 - 2. No preformed amboceptors, but increased capacity to manufacture such, by prophylactic injection.
- (b) Passive immunity.
Specific amboceptors in the blood (derived from another animal).

Complement Deviation and Fixation.—When complement is bound in such manner that it cannot enter into combination with antigen and amboceptor in bacteriolysis or cytolysis, it is said to be “deviated” or “fixed.” The terms, however, are used for slightly different conditions. If more antibodies be employed in tests or injections than the antigen can use, the excess combines with complement and prevents it from acting with the antibodies bound to the antigen. This is *complement deviation*, and of slight moment here, except to be contrasted with *complement fixation* as a diagnostic procedure. If the serum of rabbits immunized against sheep erythrocytes be mixed with sheep red cells in the presence of complement derived from normal guinea-pig serum, hemolysis results. When, however, complement is absorbed, as now to be shown, hemolysis will not occur. A mixture of the serum of a person suffering from a micro-organismal disease, an emulsion of the causative microbe, and guinea-pig serum containing complement results in the solution of the germs, *i. e.*, bacteriolysis, because the three factors—antigen, amboceptor, and complement—are present and are bound together. If, now, we were to add to this same mixture the antiserum of rabbit serum and the sheep cells, no solution of the hemoglobin would result because the complement has been *fixed* by the first combination. This is the principle of the Wassermann reaction in syphilis. It can be and is used chiefly for determination of the presence of antibody in the blood of infected persons. The application to syphilis will be discussed later. We refer to works on immunology for deeper consideration.

Anaphylaxis or **hypersusceptibility** is a condition of increased or altered susceptibility of the animal organism to foreign protein. In a sense, then, it is a condition opposed to immunity, although in some cases it may act to protect the body against infection. The term *allergie* has been suggested by von Pirquet to express the altered and usually increased property of the body to react to foreign protein.

Hypersusceptibility may be natural or acquired. The former is exemplified by the susceptibility of certain persons to pollen in rose-cold and hay-fever, or to fish and oysters which is shown by skin eruptions. Acquired hypersusceptibility is expressed when the body, once having received a foreign protein, is exposed to it a *second* time. For example, if a guinea-pig receive a small dose of horse serum, no symptoms will arise, but when a somewhat larger second dose is given, after an incubation period of eight to ten days, it will almost immediately become depressed and nervous, scratch its nose, develop violent dyspnea, and die; the fatal outcome occurs usually within an hour, but may appear in a few minutes. Upon postmortem examination there will be found spastic dilatation of the pulmonary alveoli of local and central origin, hemorrhage into and ulceration of the gastric mucosa, and scattered petechial hemorrhages. The death is due to respiratory failure, as the heart continues to beat after respiration has ceased. This sudden and violent reaction is called "anaphylactic shock," a condition most clearly expressed by the guinea-pig, which animal seems to exhibit the most pronounced reactions in allergic tests. Any animal, however, is capable of anaphylactic phenomena, and the symptoms, signs, and pathology are similar in all. The reactions differ in degree, of course, depending upon the amount and nature of protein injected, the incubation period, and the receptivity of the animal. If the amount of serum injected the second time into the guinea-pig be too small, or if introduced so that the absorption is quite slow, symptoms will be delayed, milder, and may not proceed beyond nervousness and scratching. If the dose be given into the skin instead of under it or into the circulation, only a *local* reaction of redness and edema may be occasioned. The injection first given is called the *sensitizing* dose; the second, the *intoxicating* dose.

In the discussion of infection and allergic given below it will be seen that previous exposure to a protein (bacterial) acts as the first dose, while the place of the intoxicating dose is taken by the protein (bacteria) from which the infection immediately arises.

Hypersusceptibility is specific, that is, an animal will be intoxicated only by the protein with which it has been sensitized. Guinea-pigs may be sensitized to several proteins and react specifically to each. The allergic state is transmissible to young from the mother only; if the father only be sensitized the offspring does not inherit the condition. During the anaphylactic reaction there will be found leukopenia with eosinophilia, lengthening of the blood coagulation time, and a fall in blood-pressure.

The allergic state is sometimes seen in human beings after the injection of antisera, notably diphtheria antitoxin. The reaction takes the

form of "serum sickness" or anaphylactic shock. Serum sickness occurs after an incubation period of a week to ten days, and is characterized by nervous depression, skin irritation, urticarial eruptions, fever, and malaise; occasionally the condition may be quite severe, appearing like an acute general infection. Anaphylactic shock in human beings after serum injections is similar to that outlined for guinea-pigs, and death may ensue in a few minutes. The vast majority of cases in which this acute reaction has been observed have suffered from asthma. In this connection an explanation has been sought in the fact that the anaphylactic reaction sets up spasm in involuntary muscle; that the muscles of the bronchi are contracted and shut off the alveoli.

Allergie also explains the responses obtained when the skin of a person suffering from an infectious disease is inoculated with some of the virus of that disease. This phenomenon is exemplified by the skin reaction against tuberculin exhibited by the tuberculous, and the luetin reaction in syphilitics. It is a *local* manifestation of general anaphylaxis.

There is a general tendency now to use this anaphylaxis, or the allergic state, to explain the contraction of infectious disease. It is assumed that when a person contracts such a disease he has been susceptible to the organism as an individual peculiarity, or has been prepared, sensitized, in some way.

One explanation of this phenomenon asserts that the body is unprepared for protein introduced at other places than the alimentary tract, and must prepare a ferment against it. This it does after the first dose, but in accord with Weigert's overproduction theory, it produces a superabundance of this ferment, which, when acting upon the second dose, breaks it up so quickly that various digestion products are thrown on the organs suddenly and poison them. Another theory assumes that toxic protein circulates in the blood after the first dose; the body cells are poisoned by it, but gain an affinity for it, so that they attract it in large quantity after the second injection, being then fatally injured. Friedberger views the anaphylactic reaction as the effect of toxic proteins upon cells through their sessile receptors, thus permitting a direct injury to the cell protoplasm. It is not until several injections have been given that receptors are freed and combine with toxic substances, apart from cells. This is in accord with Ehrlich's theory that cells are vulnerable in proportion to the number of their sessile receptors.

Friedberger has used the principle to develop his *anaphylotoxin* theory of infection. He assumes that an organism circulating in the body combines with the antibodies it has stimulated. This combination is then rendered toxic when acted upon by complement. Jobling goes further than this, asserting that bacteria absorb the unsaturated fatty acids of the blood, which hold in check the tryptic power of the serum, permitting the serum to break up bacterial and natural proteins and allowing escape of their toxic elements.

Vaughan believes that the invasion of the body by bacteria stimulates a ferment which, acting upon the organisms, frees their toxic protein. The ferment is specific for the infecting germ and will react

quickly when this enters the body the second time. The toxic fraction of all bacteria is the same. He explains infection and allergy on this basis. The specific antibodies are stimulated by the specific protein, so that typhoid bacilli have their own, pneumococci theirs, etc. It certainly seems that the anaphylactic state is due to degradation products of proteins and that the substances giving rise to it are complex proteins. The body fluids seem to react to the parenteral introduction of proteins by the elaboration of ferments having the power to break down these substances into simpler combinations like the amino-acids. Abderhalden has shown that in the serum of pregnant women there are ferments capable of digesting placental tissue. It may be that all immunity phenomena are protein reactions on the part of the body.

Chemistry of Antigens and Immune Bodies.—The exact composition of the various elements that have been brought to light by immunity researches is not known. Some observers maintain that only proteins can give rise to the immunity phenomena, but others believe that some lipoids and glucosids can act as antigens. No substances simpler in composition than peptones seem able to act as antigens. Judging from the work of Vaughan and Abderhalden upon bacterial and other protein intoxication, the defenses of the body seem all to be directed against foreign protein. These proteins are specific, in that protection or susceptibility toward one will not protect or dispose toward another. The various substances in the serum involved in immunity or allergy are precipitated with protein fractions, seem inseparable from them, and cannot be obtained in a pure state. The method of action, be it chemical, mechanical, or electrolytic, is not known. It might be well to emphasize here that in speaking of this parenteral introduction of protein a substance foreign to the tissue is implied.

Meiostagmin Reaction.—This is a test for showing the reduction of surface tension by the combination of antigen and specific antibody. For this purpose Traube's stalagmometer, an instrument to determine the number of drops in a given bulk, is used. If homologous antibody and antigen are mixed and incubated at body temperature for two hours, there will be found an increase of drops over the number determined before incubation. Some have used this test as an argument for the physicochemical explanation of immune reactions. Its significance is not yet fully understood.

CHAPTER IX

DISEASES DUE TO BACTERIA

THE bacterial diseases form a large and increasing group. In some cases it has been shown by the positive application of Koch's rules (see p. 37) that the suspected micro-organisms are the actual causes of the diseases under consideration; in more numerous instances all of the rules cannot be applied, but other considerations go far toward establishing the specific nature of the suspected bacteria; in still other cases the evidence warrants a strong suspicion of the pathogenicity of bacteria found in connection with certain diseases, but there is nothing approaching actual demonstration.

DISEASES DUE TO COCCI

SUPPURATIVE DISEASES

Definition.—Under this heading we include for the present various forms of suppurative inflammation, such as furunculosis, abscess formation, and allied diseases, like osteomyelitis, endocarditis, cellulitis, etc.

Etiology.—Numerous organisms have been found to have the power of producing suppuration (*pyogenic organisms*). Among these the staphylococcus group is most important. The *Streptococcus pyogenes* *seu erysipclatis* is also of great significance; less frequently the *Diplococcus pneumoniae*, the pneumobacillus of Friedländer, the *Bacillus pyocyaneus*, the typhoid bacillus, the *Bacillus coli communis* or the *Bacillus pyogenes fetidus*, the gonococcus, and others. Some cases of suppurative disease are due to a single organism; in many there is double or multiple infection.

1. **The Staphylococcus Group.**—Among these have been described three important forms: the *Staphylococcus pyogenes aureus*, *albus*, and *citreus*.

The *Staphylococcus pyogenes aureus* is a minute, rounded body about 0.5 to 1 μ in diameter, having no motility and not forming spores. When found in the tissues the cocci are apt to be associated in clusters, whence the term "staphylococcus." Sometimes they are grouped in pairs, and may thus present a resemblance to gonococci. The opposed surfaces, however, are flat instead of concave, as is the case with the gonococci. The staphylococcus may be stained with ordinary anilin solutions and is beautifully demonstrated by Gram's method. Cultures are easily obtained upon the ordinary media. The most characteristic growth is that upon agar. Along the line of inoculation a moist

colony develops, with at first a whitish but soon an orange-yellow color, especially under the influence of light. The growth in gelatin causes rapid liquefaction and the precipitation of orange-yellow particles. The growth is best obtained at oven-temperatures (25° to 35° C.; 77°–95° F.), but may be secured at lower degrees.

Distribution.—The *Staphylococcus aureus* is frequently found upon the skin or in the various external secretions of healthy individuals. It does not seem to flourish anywhere apart from the bodies of men or animals, but may remain in an active state in the dust of rooms or upon clothing and the like. It has been found in various lesions of the body, notably, however, in furuncles, abscesses, and carbuncles, and in ulcerative conditions of the exterior or of the mucous membranes. It is also frequent in internal suppurative inflammations, such as malignant endocarditis, osteomyelitis, appendiceal abscesses, etc. In many of these lesions other organisms may be associated.

Pathological Physiology.—Filtrates of the cultures and the bodies of the staphylococci (killed by heat) contain highly toxic substances capable of producing intense inflammation and suppuration. Certain of their products are markedly hemolytic.

When injected into the subcutaneous tissue the staphylococcus produces local effects. The organisms may become liberated, gain entrance to the circulation, and produce widespread results; but it does not seem to produce extracellular toxins that cause generalized results. The effects of the staphylococcus seem to be due rather to a certain poisonous body contained in the organism itself. This has been termed "bacterial protein," and it has been thought to belong to the group of alkaline albuminates. This body by its chemotactic effect causes the leukocytic accumulations found in suppurative inflammations. The staphylococcus also leads to liquefaction in the tissues, as in gelatin, both directly and through the accumulation of bodies derived from leukocytes. The defence of the organism against the staphylococcus is partly mechanical and partly vital. The leukocytes probably englobe a certain number of organisms and cause their destruction, while soluble bactericidal bodies seem to be produced in the course of the infection.

Injection of cocci gives rise to antibodies—agglutinins, opsonins, and bacteriolysins. Upon them depends the use of bacterin or vaccination treatment.

Pathogenicity.—When virulent cultures are injected into animals, abscesses are produced and a fatal termination may follow. In the latter case dissemination through the blood is found, and infarcts of the kidneys, lungs, and other organs caused by bacterial emboli are discovered. Multiple abscesses may be seen. The organism readily loses its virulence, as in the case of those found upon the skin of healthy persons and in other accidental situations. When rubbed in a virulent state into the skin of man it produces abscesses or boils. It may remain dormant within an enclosed abscess or sequestrum in a bone, or apparently in a subacutely inflamed heart valve or muscle, and light up upon some secondary infection. Staphylococcus infection tends to remain local, with

occasional spread to the circulation. Its local lesions are of slower progression than those of the streptococcus. Its presence sometimes favors the growth of other organisms, notably the influenza bacillus.

Staphylococcus pyogenes albus (Fig. 99).—This organism is practically identical with the last-named in morphology, but in culture produces a white instead of a yellow growth. One of its forms has been found as a frequent harmless parasite of the skin (*Staphylococcus epidermidis albus* of Welch). It occurs in abscesses and various suppurative diseases, but rarely alone. As a rule, it is associated with the golden staphylococcus or other organisms. It is distinctly less virulent than the *aureus*.

Staphylococcus pyogenes citreus.—This form is the least important of the three. It is not so common and, as a rule, less virulent. It differs in the brilliant lemon color obtained upon culture in various media.

2. **The Streptococcus pyogenes seu erysipelatis**.—Under the name *streptococcus* are included various spherical bacteria which divide only

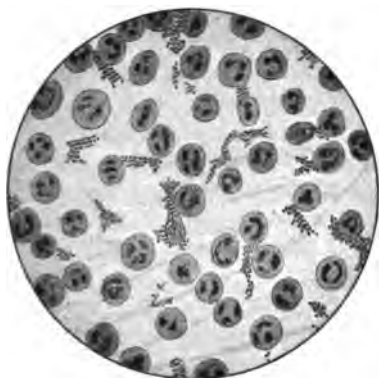


Fig. 99.—*Staphylococcus pyogenes albus* (Jakob).

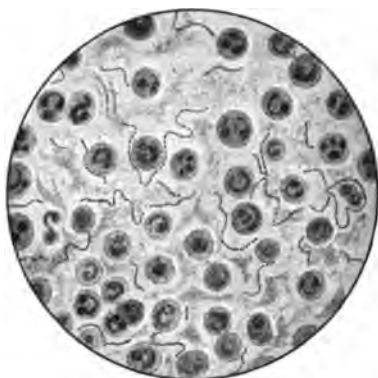


Fig. 100.—*Streptococcus pyogenes* (Jakob).

in one plane and form chains of varying length. The different forms resemble each other so closely that some authors group them all, including the *Streptococcus pneumoniae*, under one general head. The last, however, seems sufficiently differentiated to merit separate classification.

The *Streptococcus pyogenes* was first studied by Rosenbach in cases of suppuration. A similar organism was afterward described as the *Streptococcus erysipelatis* by Fehleisen. It would seem, however, that these two organisms are identical. The streptococcus is a small spherical organism of variable size ($0.5-1\ \mu$), frequently associated in chains of from three to twenty or more individuals (Fig. 100). Not rarely it occurs in diplococcus forms (as pairs). It is easily stained with ordinary anilin solution or by Gram's method. The cocci are not motile. Spore formation has not been observed, but occasionally in chains one of the individual members is larger than the rest, suggesting arthrospores. Upon artificial media scanty but rather characteristic growths are ob-

tained. On the gelatin plate there are formed small, translucent, whitish or yellowish colonies of irregular outline. The gelatin is not liquefied. Upon agar a very thin, transparent growth forms around the line of inoculation. It consists of separate colonies which usually do not coalesce. On mixed agar and blood plates the colony of the true streptococcus produces a pale gray dot surrounded by an area of hemolysis. Certain varieties lack this power. In milk the growth is usually abundant and attended with lactic acid formation and coagulation of the casein.

In the species *Streptococcus pyogenes* there are several varieties that have been found so frequently under special conditions that they seem worthy of separate mention. The principal one is the *Streptococcus viridans*, which is common in streptococcal endocarditis. It is not hemolytic and grows in green colonies on blood-agar. *Streptococcus mucosus* is a mucus-producing organism found usually in the throat or in enclosed abscesses. The streptococci of the feces have minor peculiarities differing from the true type. Another variety seems to have a predilection for joint cavities (*Streptococcus rheumaticus*).

It has been asserted by Rosenow that the members of the streptococcus-pneumococcus group are but variants of one species, and he claims to have been able to follow a mutation from one to another under artificial conditions. Under prolonged artificial cultivations these organisms do surely lose some minor characters, but mutation must be stationary to be actual.

The *distribution* of the streptococcus is much the same as that of the staphylococci, though it is less commonly discovered about the healthy body. It may, however, be found upon the mucous membranes or in the various secretions or excretions of the body. It is probably a strict parasite, multiplying only within the living organism.

In disease it has been found in various forms of suppuration, such as phlegmonous forms of inflammation of the subcutaneous or submucous tissues, either alone or in association with other organisms. It occurs occasionally in focal suppurations, such as abscesses, though these are more commonly due to staphylococci alone. The streptococcus occurs at times in ulcerative endocarditis, not rarely in infectious endometritis and in generalized septicopyemia. Streptococcic inflammations of the throat are of great interest. They may occur in persons previously in good health, or in the course of infectious diseases, like scarlatina, measles, or influenza. To the clinician the resulting lesion may be indistinguishable from that of diphtheria; bacteriological examination alone serves to establish the diagnosis. Deep involvement of the tonsil is one infection-atrium for the cocci to enter the blood. Following such an entrance we may have serous membrane involvement, particularly in the heart valves. The streptococcus is found in all cases of erysipelas in the tissues and in the other exudations.

Pathological Physiology and Pathogenesis.—The streptococcus seems to be more active in the production of soluble toxins than staphylococci. The *toxin* has been made by inoculating small quantities of

bouillon with virulent cocci, allowing these to grow for several weeks, and then destroying the organisms by heat. The injection of the toxins thus produced leads to local and general reaction. While there is a certain amount of this extracellular toxin, it seems that most of the toxic substances of streptococci are embodied in the micro-organism itself. In virulent cultures actively hemolytic bodies are often present, and certain streptococcic infections in man are attended with hemorrhages and evidences of hemolysis.

The principal pathological character of streptococcal infections is their spread. Instead of localizing like the staphylococcus, a diffuse spreading inflammatory edema results with involvement of lymphatics and blood-vessels, by either of which routes the cocci get into the blood-stream. Serous membranes are especially susceptible to streptococci, and thrombophlebitis or arteritis is the first lesion arising when the germ reaches a vessel. In these infections there is more often bacteremia than is the case with staphylococci.

Injected into animals (intravenously) virulent streptococci may occasion septicemia, but it is notoriously difficult to obtain cultures of great virulence and the succeeding generations soon lose their power. White mice and rabbits are the most susceptible animals.

A single attack of erysipelas or streptococcic infection confers no immunity on man and, similarly, one inoculation occasions no immunity in animals. By repeated injections, however, an *antistreptococcus serum* of some potency has been obtained. Recent studies show that more satisfactory practical results may be obtained when the antistreptococcus serum has been prepared with a strain of organisms similar to that present in the case under treatment. For this reason mixtures of serum prepared with several strains are used (polyvalent sera), so that in a clinical case (because of the difficulty in distinguishing various strains) a specifically active antiserum may be administered. The efficacy of such polyvalent sera, however, is somewhat doubtful.

Streptococcus intracellularis meningitidis (Weichselbaum).—This organism, also called *meningococcus* or *Diplococcus meningitidis*, is found in the meningeal pus, in the blood, nasal mucus, sputum, and urine of individuals affected with epidemic cerebrospinal meningitis. This micro-organism in some respects resembles very closely in its form and intracellular occurrence the gonococcus.

The organism appears as a biscuit-shaped diplococcus, irregular in size, sometimes occurring as tetrads or in clumps, and occasionally as short chains in which the line of cleavage between the diplococci is in the same direction as that of the chain. The coccus is Gram-negative, but here and there will be found a few units that retain the blue of the gentian-violet. It is easily stained with Löffler's methylene-blue.

In the meningeal exudates it is usually found within polymorphonuclear leukocytes, like the gonococcus. Some have described its occurrence within the cellular nuclei; this is doubtful.

It grows well at 37.5° C. (100° F.) on blood-agar, serum-agar, and plain agar. On the latter there appear, in forty-eight hours, flat.

grayish-white, faintly granular and viscid colonies that do not coalesce. On blood-agar the colonies are more luxuriant.

The cultures may live for weeks, but often die in a few days, and, therefore, require frequent transplantation.

Distribution.—The meningococcus is found in the seropurulent exudate of epidemic cerebrospinal meningitis and is readily demonstrated in the fluid obtained by lumbar puncture. It has frequently been found in the nasal mucus of patients suffering from the disease and in healthy individuals more or less closely associated with the patient. The assumption is, that the meningeal infection occurs by passage of the organisms through the lymph-channels from the nose or sinuses adjacent to the meninges. Recent experiments seem to indicate that the organisms may travel in the opposite direction, for in monkeys infected by intradural inoculation the organisms were found in the nasal cavities after a short interval. Organisms resembling the meningococcus and probably actual meningococci have been found in the lungs in cases of bronchitis and pneumonia complicating epidemic meningitis.

Pathological Physiology and Pathogenesis.—Large subcutaneous injections may cause death, and intrapleural and intraperitoneal injections may kill animals and cause a fibrinopurulent inflammation of the serous membrane. Subdural inoculation (spinal and cerebral) in dogs and monkeys have caused lesions identical with those found in man.

The toxins of the meningitis coccus are endocellular and are freed *in vitro* by autolysis. Agglutinins and lysins are developed in patients and experimental animals. Flexner, Jobling, and Wassermann have developed an antiserum from goats which when used intraspinally dissolves the organisms.

Other Organisms in Meningitis.—The pneumococcus, Streptococcus pyogenes, Staphylococcus pyogenes, typhoid and colon bacilli, influenza bacillus, and, less commonly, some other forms have been isolated in cases of primary meningitis or meningitis secondary to infection elsewhere.

GONORRHEA

Definition.—Gonorrhea is an infectious inflammation of the urethral or other mucous membranes due to a specific organism, the *Micrococcus gonorrhæe* or *gonococcus* discovered by Neisser in 1879.

Etiology.—There is no doubt that the gonococcus is the specific cause of gonorrhea. This organism is a micrococcus, usually arranged in pairs, the opposed surfaces of each being slightly concave. This arrangement has suggested the designation "biscuit-shaped" diplococcus (Fig. 101). Sometimes groups of four or more are found, while in other cases the cocci occur singly. The organisms are abundant in the pus of acute gonorrhea, less abundant in advanced stages, in the pus of gonorrheal salpingitis or other conditions, and may not be discovered at all. They generally occupy the pus-cells, lying in the proto-

plasm, either in small numbers or so abundantly as to fill the cell uniformly. In the tissues the same intracellular position is usual, but here, as in the free pus, some organisms may generally be found between the cells. The gonococcus stains readily with ordinary solutions of anilin dyes, and is distinctly Gram-negative.

Cultivation of the gonococcus is difficult. Growths may, however, be obtained at 37° C. (98.6° F.) upon agar-agar streaked with human blood or on media prepared from human ascitic or pleuritic fluid or albuminous urine. Later generations may grow well on ordinary media, but usually require the serum additions. The growth in blood-serum consists of small colonies of grayish color that coalesce and form a film on the surface of the medium; around the colony may generally be seen an irregular and inconspicuous extension.

The gonococcus cannot be positively distinguished by its morphology nor by the intracellular position. Other organisms may in certain stages of their growth show a typical biscuit form (staphylococci and others); and the intracellular position is not rarely assumed by a variety of bacteria. The failure to stain by Gram's method and the failure to grow on ordinary media are strong points suggesting the gonococcus. Typical cultures alone establish the diagnosis. A number of organisms resembling the gonococcus were found by Bumm in the vaginal mucus. The *Micrococcus catarrhalis* also resembles it closely. No similar micrococcus has thus far been found in the male urethra.

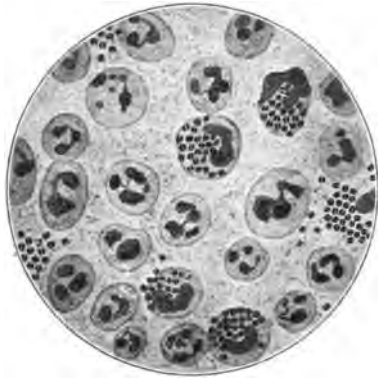


Fig. 101.—Pus from gonorrhea, showing gonococci (Jakob).

Pathogenicity.—It has been demonstrated by direct implantation of pure colonies upon the healthy urethra that this organism will cause characteristic gonorrhea. Urethritis may, however, be due to other organisms; the specific form termed "gonorrhea" is probably always due to the gonococcus. Secondary lesions, such as salpingitis, oöphoritis, arthritis, peritonitis, conjunctivitis, endocarditis, etc., may also be due to this organism, no other form of bacteria being present. Sometimes, however, complications, such as periurethral abscesses, suppurative adenitis, etc., are due to secondary infections.

Gonococci stimulate the formation of slight amounts of agglutinins, opsonins, and bacteriolysin. Antisera are of little value, but bacterins or vaccines may be useful. The toxin is intracellular.

Pathological Anatomy.—The lesions of gonorrhea will be considered elsewhere. Suffice it to say in this place that the organism causes suppurative catarrh of the mucous surfaces with which it comes in contact. There is abundant cellular exudation and the organisms tend to penetrate deeply into the tissues.

Pathological Physiology.—Gonorrhea is in most cases a purely local disease. Little is known of its power to produce soluble toxins. The effects are probably due to an intracellular toxin. The distant lesions are in all cases, as far as we definitely know, dependent upon transportation of the specific organism. These have been found in the effusions of arthritis, in meningeal exudates, and in the vegetations of gonococcal endocarditis, as well as in the blood in the last-named condition.

CROUPOUS PNEUMONIA

Definition.—There are a number of forms of inflammation of the pulmonary tissues to which the term “pneumonia” is applicable. The most definite form of disease is that spoken of as croupous, fibrinous, or lobar pneumonia. In its typical form this is a specific and well characterized disease. It is infectious, more or less contagious, and caused by a specific organism.

Etiology.—The organism most frequently found in the lung in croupous pneumonia and doubtless the specific cause of the disease in such cases is the *Diplococcus pneumoniae*, belonging to the genus *Streptococcus*. It is less regularly the etiological agent in bronchopneumonia and atypical pneumonias, but even in these cases it is found more frequently than other bacteria.

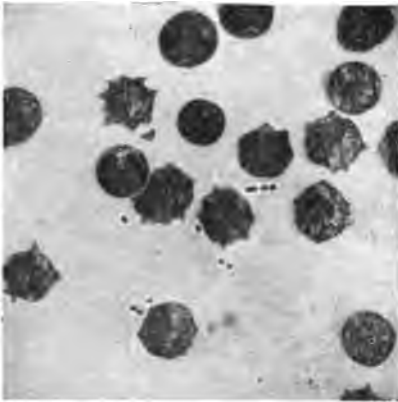


Fig. 102.—*Diplococcus pneumoniae* in the blood (Fränkel and Pfeiffer).

The organism is also called the *pneumococcus*, the *Micrococcus lanceolatus*, and sometimes the *Streptococcus pneumoniae seu lanceolatus*. The diplococcus of pneumonia was recognized in the saliva of healthy persons by Sternberg and Pasteur, but its relation to croupous pneumonia was first demonstrated by Fränkel, and later by Weichselbaum. The individual organism has a somewhat elongated, lanceolate shape, and has, therefore, been considered a bacillus, though it does not always show this

pseudobacillary shape distinctly (Fig. 102). In the sputum and lungs and in the blood of inoculated animals it is commonly found in pairs; the broader ends of the organisms adjacent, and the pointed ends projecting outward; the group is surrounded by a transparent capsule, which does not readily take stains and, therefore, becomes conspicuous (Fig. 103). Sometimes the organism forms chains, in which, however, the pairs of micrococci are a little distance apart. Chain formation is especially marked when the organism is grown in fluid media. The capsule is not seen when the organism is obtained from cultures. The diplococcus does not possess individual motility and has no flagella. It does not seem to produce spores.

It may be readily demonstrated in the sputum or in the tissues by staining with the ordinary anilin dyes or by Gram's method.

Cultivation.—The diplococcus grows readily upon ordinary media, excepting potato. It forms characteristic colonies upon agar-agar plates or in gelatin. Upon the surface of the agar there appear transparent drop-like colonies hardly visible to the naked eye, which under the microscope have a finely granular appearance. Upon gelatin plates similar growths are produced, while in gelatin punctures the growth occurs along the path of the wire as granular whitish spots separated from each other. The addition of serum or ascitic liquid to agar makes a medium in which larger and more conspicuous grayish colonies of circular outline appear on the surface. In the paler marginal zone of the colony, diplococci or short chains may be seen. On blood-agar pneumococci produce small round greenish colonies without hemolysis. In bouillon a cloudiness is produced when the culture is from twelve to twenty-four hours old; later the organisms precipitate and the bouillon becomes clear. Milk is acidified and at times coagulated by the pneumococcus. When inulin is added to a serum medium the pneumococcus ferments the inulin and coagulates the serum. The organism tends to die out very readily in cultures, and also loses its pathogenic property when propagated for several generations. In solid media containing serum and more particularly in fluid media the virulence may be preserved for a long time, sometimes for months. It is most luxuriant at 37° C. (98.6° F.). Pneumococci are dissolved by bile or solutions of its salts, in this being different from the streptococci.

Pathogenicity.—The specific character of this organism has not been definitely proved according to the rules of Koch, but it is highly probable that it is the usual cause of pneumonia. The diplococcus is frequently found in the saliva of healthy persons. When this is introduced into animals, particularly rabbits, the animal dies, with evidences of rapid sepsis (sputum septicemia). The postmortem shows some fibrinous exudate and occasionally a little pus at the point of inoculation. The spleen is enlarged, and capsulated bacteria of distinct lanceolate form are widespread throughout the body. Injections of lung tissue or of pneumonic sputum produce similar results, and the organism in pure culture likewise causes this form of septicemia. It has been shown that injection of pneumonic exudate aspirated from the consolidated lung into the lungs of rabbits will produce true pneumonia. Typical pneumonia has been produced by injection of virulent pneumococci into the lungs of rabbits previously immunized against the pneumococcus to prevent the occurrence of general pneumococcus septicemia.

The most successful attempts at producing pneumonia were made

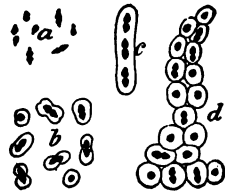


Fig. 103.—*Diplococcus pneumoniae*: a, Cocci, without capsules; b, single and paired cocci, with capsules; c, chain form; d, colony of cocci (Ziegler).

by Rosenau and later by Meltzer, who atomized pneumococcus cultures into the trachea of dogs.

The toxin of the pneumococcus is intracellular. Some antibodies may be formed.

Besides the diplococcus there are certainly other elements which contribute to the causation of the disease, else the frequent occurrence of the micro-organism in question in the saliva would make pneumonia a much more common affection. The nature of the contributing causes is, however, obscure. Exposure to cold, general depression of the system, traumatism, alcoholism, and other causes certainly predispose or help to determine the occurrence of the disease. These causes may act by temporarily increasing the virulence of the diplococcus or by lowering the resistive power.

Certain irregular forms of lobar pneumonia may be caused by streptococci, staphylococci, the *Bacterium pneumoniae* of Friedländer, the influenza bacillus, that of typhoid fever, etc.; but true croupous pneumonia is probably always due to the *Diplococcus pneumoniae*.

Pathological Anatomy.—(See Diseases of the Lungs.)

Pathological Physiology.—The diplococcus produces, in the first place, local lesions of the lungs; and in the second place, systemic infection and possibly also general intoxication by toxins of uncertain character. The infection-atrium is almost always the respiratory tract. In the case of systemic infection the organism itself gains access to the blood and may produce secondary lesions in other organs. Infection with the diplococcus of pneumonia causes a pronounced reaction on the part of the blood in the form of leukocytosis. This is not invariable, but is usually seen. After the attack of pneumonia there is temporary immunity, and it has been found that animals may be immunized for considerable lengths of time by repeated injection of pneumococci. The serum of the immunized animal has a certain protective and curative value which has recently been attributed to the formation of opsonins, which are operative by rendering the pneumococci liable to rapid ingestion by phagocytes.

There are several varieties of the pneumonia coccus with slightly differing biological characters, and it may not be possible to obtain a therapeutic antiserum against them all. Cole insists that a polyvalent serum will not answer, but that one should use an antiserum against the type of pneumococcus present in each individual case. The antiserum supplies immune bodies including, perhaps, antitoxin. The author just mentioned has been able to divide the pneumococci into four main groups into which practically all strains fall. For two of these he has a separate antiserum. It has also been possible to use with advantage as a therapeutic agent autolysates of pneumococcus cultures at that stage of autolysis when the specific protein is freed.

The Diplococcus in Other Diseases.—The *Diplococcus pneumoniae* has been found in various conditions complicating pneumonia, and occasionally in lesions unassociated with croupous pneumonia. Among other lesions, meningitis, pleurisy, and other inflammations of the

serous surfaces, abscesses, otitis media, and arthritis have been found to be due to this organism; or, at least, this organism alone has been found in some of these cases. Endocarditis is frequently caused by the pneumococcus. It may be primary or secondary.

OTHER FORMS OF PNEUMONIA

Among other varieties of pneumonia may be mentioned the catarrhal or lobular form, the tuberculous form, and various irregular pneumonias, partly cellular, partly fibrinous, partly purulent or hemorrhagic. Though the pneumococcus is more frequently present than any other single organism in bronchopneumonias after infectious diseases like measles and diphtheria and in various irregular types of bronchopneumonia, different organisms may be found in such cases, and some of these may be of etiologic importance in certain cases. Not rarely the pulmonary disease is the result of mixed (double or multiple) infection.

Bacterium pneumoniæ of Friedländer.—This organism was regarded at one time as the cause of croupous pneumonia. It prob-

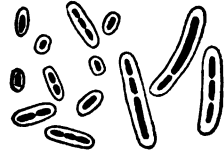


Fig. 104.—Bacterium pneumoniæ of Friedländer.

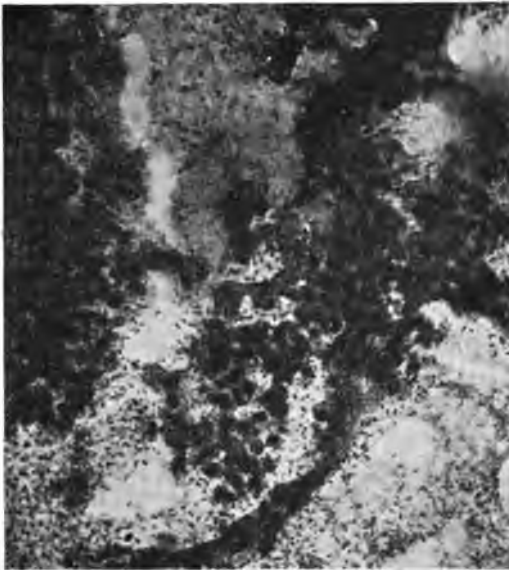


Fig. 105.—Friedländer's pneumonia, showing the enormous number of bacteria in the exudate.

ably occurs in most cases as a mixed infection, though it may occasionally be the cause of catarrhal or irregular forms of pneumonia or of ordinary croupous pneumonia. With this organism also Meltzer has been able to produce pneumonia in dogs by atomized insufflation.

The cases of pneumonia due primarily to the pneumobacillus are characterized by their virulence and a peculiar viscid character of the exudate in the lung. Friedländer's organism occurs as a distinct bacillus, usually in pairs and surrounded by a capsule like that of the diplococcus (Fig. 104). Sometimes it may form chains of three, four, or more organisms. It stains well with the anilin dyes, but is decolorized by Gram's method. A characteristic culture is obtained in gelatin. The puncture-culture is characterized by a luxuriant growth at the top and a considerable vegetation all along the track. This leads to a nail-shaped growth. The gelatin does not liquefy. Upon agar a considerable whitish or yellowish moist growth occurs upon the surface. There is formation of gas in media containing glucose, and often also on potato.

A number of organisms closely related to Friedländer's pneumobacillus have been classified under the generic name *Bacterium mucosum capsulatum*. Among these are the *B. lactis aërogenes*, *B. acidi lactici*, *B. ozænæ*, and *B. rhinoscleromatis*. The several types differ somewhat in their power to ferment various carbohydrates.

Other Organisms in Pneumonia.—Among the various organisms that have been found in bronchopneumonia or less commonly fibrinous pneumonia are the *Streptococcus pyogenes*, more rarely the influenza bacillus, the *Bacillus coli communis*, the typhoid bacillus, the bacillus of glanders, of the plague, and occasionally other organisms. In some of these cases the disease may be the result of double infection.

Tubercle Bacillus.—A uniform pneumonic process may be due to simple infection with the tubercle bacillus, or to mixed infections.

Micrococcus tetragenus.—This form is a Gram-positive micrococcus from 1 to 2 μ in diameter, and receives its name from the peculiar association in groups of four. It occurs in the sputum and contents of cavities in pulmonary phthisis, and occasionally elsewhere. It may give rise to general sepsis.

Micrococcus catarrhalis is a micro-organism found by Pfeiffer in cases of bronchitis in which there was a great deal of expectoration, and in which the symptoms resembled those of influenza. It is a small coccus, usually occurring in diplococcic form, and resembling the micrococcus of gonorrhea. It often is seen within the pus-cells, and occurs in large numbers in the sputum and nasal secretion of individuals suffering from bronchitis. It does not cause the constitutional disturbance that is caused by the bacillus of influenza, but is often found as an associated infective agent in cases of pneumonia due either to the *Diplococcus pneumoniae* or to the bacillus of influenza. To obtain it in pure culture it is best grown on blood-agar. It grows as sharply defined, somewhat raised, granular, yellowish, non-transparent colonies on the surface of agar. It resembles the *Staphylococcus pyogenes aureus*, but the colonies are much more raised and harder. They can be picked up on the end of the needle, and are crushed with difficulty. The needle can be drawn across the culture without destroying the integrity of the individual colonies. After the first generation the micrococcus grows well on

ordinary agar, but it must be transferred every three or four days to be kept alive. It is decolorized by Gram's method. Its pathogenicity is as yet undetermined. In its behavior toward animals it resembles the bacillus of influenza. It seems to be of importance in the pneumococcal or streptococcal anginae, since, according to the work of one of the authors, a culture of one of these cocci is much increased in pathogenicity for guinea-pigs when mixed with *Micrococcus catarrhalis*.

DISEASES DUE TO BACILLARY FORMS

DIPHTHERIA

Definition.—Diphtheria is an infectious and contagious disease caused by a specific bacillus.

Etiology.—The *Bacterium diphtheriae* was discovered by Klebs, but more accurately studied by Löffler, and is, therefore, called the Klebs-Löffler bacillus. This organism is a rod varying in length from 1 to 6 μ , rather thick, and with somewhat swollen ends. It is readily demon-

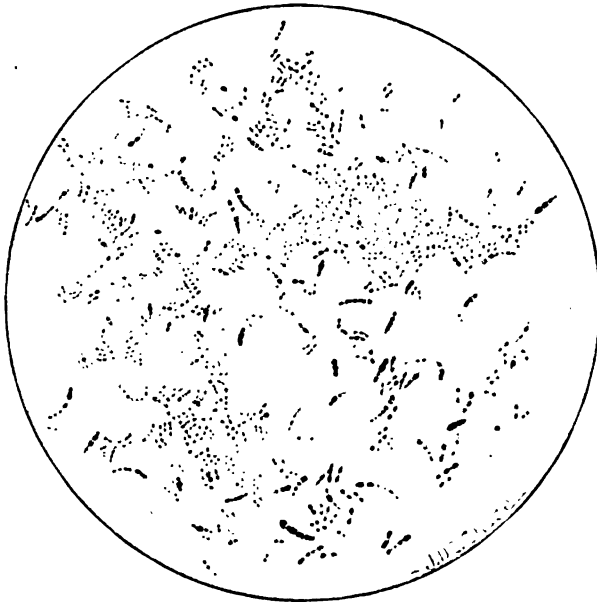


Fig. 106.—Diphtheria bacilli from an eighteen-hour blood-serum culture.

strated in the local lesions of the mucous membranes or skin, where it may be quite abundant; the individual bacilli, however, are separate from one another. The organism is peculiar in its great irregularity of shape and size, particularly in cultures (Fig. 106). Seemingly branched forms have been observed, and some investigators have viewed the organism as a streptothrix or even as one of the hyphomycetes.

Frequently one end is especially large, giving a club-shaped appearance; some of the bacilli are very large; some present rounded granules at either end, the so-called polar granules or Ernst bodies. The bacillus is readily stained with aqueous solutions of basic stains, especially with those rendered slightly alkaline. (Löffler's solution—saturated aqueous solution of methylene-blue, 30 c.c., in aqueous solution of potassium hydrate, 1:10,000, 100 c.c.—is the favorite stain.) The color is retained when stained by Gram's method. The stained specimen shows the morphology of the bacillus very clearly. The rounded ends generally stain more deeply than the shaft of the bacillus, so that the appearance somewhat suggests a diplococcus, or as a row of cocci. Not rarely transverse fractures give the organism the appearance of disjointed segments. There are no flagella, and the bacillus is not motile. Spores have not been demonstrated.

Cultivation.—The most characteristic cultures are obtained upon blood-serum, especially such as contain a small amount of glucose. Upon this medium there is formed within six, twelve, or twenty-four hours a thin, whitish or yellowish-white layer of irregular outline, often showing separate smaller colonies around the edge. A small portion of the colony may be removed and stained, and the diagnosis thus established with ease in a short time. Other organisms found in the throat are slower in growth, and do not, therefore, interfere with the diagnosis.

Pathogenicity.—When cultures in bouillon are injected beneath the skin of a guinea-pig a fibrinous inflammation with more or less widespread edema results, and the animal dies in from twenty-four to thirty-six hours. Congestion of the adrenal, necrotic foci in the liver and other organs are found postmortem; the neighboring lymphatic glands are enlarged. If the animal survive, paralysis may make its appearance, as in human beings recovering from the disease. The pathogenicity has also been shown by inoculation of various other animals, and definitely by accidental infection of man.

Klebs-Löffler bacilli may be found in the pharynx of a person showing no indication of disease. This indicates that the organism has not found a favorable soil for its development or no abrasion or opening into tissues that will support its growth. The bacillus may, however, thrive and multiply for a considerable time upon the mucous membrane of such a throat, as it may upon food, clothing, or other infected materials.

Mixed Infection in Diphtheria.—Other organisms, notably streptococci, staphylococci, and pneumococci, may be associated with the diphtheria bacillus, and may be actively concerned in the local or general pathological processes. The streptococcus is especially potent as an associated cause. The streptococcic infection may precede or follow the diphtheritic infection. Various organisms of a saprophytic nature may cause putrefactive changes in the pseudomembrane.

Predisposing Causes.—Some predisposition is necessary for the development of the disease. In part this is personal, some individuals being highly susceptible, others scarcely at all. In part, accidental

conditions, such as pharyngitis, laryngitis, abrasions, etc., furnish a favorable opportunity for the infection.

The *diphtheria of birds, calves*, and certain other animals is distinct from the human disease; and the organisms are in no way related. Human diphtheria may occur in cats, and these animals may propagate epidemics.

Pseudomembranous (fibrinous) inflammation is not invariably caused by the diphtheria bacillus (see Inflammation). Among the organisms capable of causing somewhat similar pseudomembranes, the most frequent is the *Streptococcus pyogenes*; another important one is the *pneumococcus*.

Distribution of the Bacilli.—The organisms are abundant in the pseudomembranes of diphtheria, but are only exceptionally found in the blood or internal organs. The visceral or nerve lesions are usually due to the toxins, and not to the bacillus. The same is true of experimental diphtheria. The internal lesions may be produced by injection of the toxin obtained by filtering a bouillon-culture through a Pasteur filter.

Pathological Anatomy.—Diphtheria is primarily a local disease of the pharynx (pharyngeal), of the larynx (laryngeal), of the nose (nasal), or of the skin (dermal). The bacillus lodges in the mucous membrane or skin, and produces a pseudomembrane. This consists of fibrinous exudation in the form of fine granular material or a fibrillar network, in which are embedded the epithelial cells and other tissue elements and infiltrating leukocytes. The epithelial cells rapidly undergo coagulation necrosis or granular degeneration, as do also the connective tissues when the process extends beneath the mucosa. The blood-vessels become obstructed by thrombosis or compression, and the tissue is, therefore, avascular. Nearly always the pseudomembrane thus formed is attached to the underlying tissues, and when removed a raw and bleeding surface is exposed. The depth of involvement, however, varies; sometimes the submucosa is soon involved; more often the disease is practically confined to the mucosa.

The macroscopical appearance is that of a whitish, dirty-yellowish, or brownish membrane upon the mucous lining of the throat. This begins as one or several patches upon the tonsil, and spreads rapidly to the neighboring parts. In other situations the appearance is much the same. Inflammatory swelling beneath and around the diseased area is habitual. It is of great clinical importance to recognize that true diphtheria may occur in the form of typical follicular tonsillitis.

Internal or visceral lesions may occur in the course of diphtheria or during convalescence. They are usually due to the action of the toxin, and not of the bacillus. Necrotic foci in the liver, showing advanced cellular degeneration of the cells with hyperchromatosis of the nuclei, and similar lesions of other organs, may be seen in the human body, as in animals killed with the organism or its toxin. Swelling of lymph-tissue is common, the principal point of attack being endothelium. This may go on to focal necrosis. Myocarditis and myocardial degenera-

tion, renal degeneration and nephritis, and, most interesting of all, degeneration of the peripheral nerves and neuritis may be met with. All of these will be described elsewhere. This is believed to be due to the toxone fraction of the toxin.

Pathological Physiology.—As has been said, the disease is primarily local, and the bacilli nearly always remain localized in the superficial lesions. They have been found in the internal organs, showing that they can enter the blood-stream. The *local* effects are believed by some to be due to an endocellular toxin. The general manifestations—fever, prostration, and the visceral lesions—are caused by poisonous substances elaborated by the growth of the bacilli. There are probably several substances of this sort, but one in particular—the *torin*—is most important. This may be obtained by filtering bouillon-cultures through porcelain, and by its injection the constitutional and some of the local manifestations of the disease may be induced in animals. Successive introduction of increasing doses of toxin causes the development of antitoxic substances that may finally accumulate in the blood to such extent that the animal becomes immune to the most virulent bacilli. The *antitoxic* substance or substances, or *antitoxin*, found in the blood and the blood-serum of immunized animals will render other animals immune for a time, or combat and overcome the disease if already existing. Simultaneous injection of antitoxin and of many times the ordinarily fatal dose of toxin or diphtheria-cultures leaves an animal unharmed. The value of the antitoxin in animal experimentation is beyond doubt. In the human being there is scarcely any doubt of its potency, though, of course, crucial experiments cannot be made. Experience has shown that its therapeutic use in diphtheria should never be omitted.

After an attack of diphtheria there is temporary immunity, but this passes off and successive attacks may thus occur in the same person.

Diphtheria-like bacilli are sometimes found in the pharynx of healthy individuals in some cases, as well as upon the hands, hair, or in other parts of the body. They are also found in various forms of rhinitis, conjunctivitis, and non-diphtheritic angina. These may differ from the virulent bacilli in being somewhat shorter and in growing more luxuriantly. Their distinctive character, however, is their relative harmlessness when injected into animals.

Pathogenic powers have been ascribed to certain members of the pseudodiphtheria group of bacteria. Some seem to be able to produce a transmissible angina that is not favorably influenced by diphtheria antitoxin. Others of the group may cause general infection or severe local disturbance.

The exact relationship of the members of the diphtheria group is not yet decided, but the classification of Emerson is quite good:

“(1) Bacilli with typical morphology, typical cultural characteristics, especially the ability to form acid from glucose, and which produce the typical lesions in animals, are, in the opinion of all observers, *Bacillus diphtheriæ*.

"(2) Bacilli with typical morphology and typical cultural reactions, especially the ability to form acid from glucose, but which are not pathogenic to animals, may be called avirulent diphtheria bacilli.

"(3) Bacilli with typical morphology, but which do not conform in their cultural reaction with the diphtheria bacillus, and which are not pathogenic for animals or do not produce typical lesions, may properly be called pseudodiphtheria bacilli.

"(4) Finally, there are a number of organisms which resemble *Bacillus diphtheriæ* in many ways, but whose morphology is not exactly the same, . . . and which have different cultural characteristics, and differ in their pathogenicity. This group certainly includes the pseudodiphtheria bacillus of Hoffmann, the xerosis bacillus, and others."

The pathogenic members belong in the first and third or possibly the second and third groups. A difference of the pseudo- and true diphtheria bacilli not mentioned above is that the former do not produce a soluble toxin, but upon injection excite a bactericidal serum in experimental animals specific for each variety. The so-called virulent pseudodiphtheria bacilli have been found in cystitis, septicemia, and other conditions. They are very common in mixed infections, and have been said to be more potent in continuing an infection than in inciting it.

TYPHOID FEVER

Definition.—Typhoid fever is an infectious disease, with characteristic lesions of the intestines, and due to a specific bacillus. It is important to recall the fact that local or general *typhoid infection* may occur without the intestinal lesions or usual clinical features of *typhoid fever*. In such cases local inflammatory lesions, suppurations, necroses, or septicemia have been observed.

Etiology.—Certain predisposing features make individuals more liable at one time than another to this disease. It occurs in adolescence and the young, but rarely in the old. Climatic conditions are supposed to play some part, and doubtless do have an influence. Typhoid fever is especially a disease of the temperate zones, and is most abundant in the autumn. Drainage and other conditions affecting the surroundings of persons may influence the predisposition. One attack usually confers immunity for the rest of life; exceptions, however, are met with.

The Bacillus.—The *Bacillus typhi abdominalis*, the specific organism, was discovered by Eberth and isolated by Gaffky. It is a short bacillus, from 1 to 4 μ in length and 0.5 to 0.8 μ in thickness. The ends are rounded and often somewhat plump. In culture these rods or bacilli occasionally form long chains, but in the tissues they are never so arranged. The organism is actively motile, this being due to flagella, of which there are eighteen or twenty attached to the periphery (Fig. 107). When stained with alkaline methylene-blue or other stains there are sometimes seen dark-colored spots at the ends of the organism. These were formerly regarded as spores, but are now recognized as areas of protoplasmic

condensation. Under certain circumstances the condensation is seen in the center and vacuole-like formations are found at the ends. The organism is readily stained, but decolorizes very easily, and is, therefore, difficult to demonstrate in tissue. The bacilli are, as a rule, found in clusters. These groups may, however, be few in number, and thus difficult to detect in the organs.

Cultivation.—Artificial cultures of the bacillus have been obtained from the spleen and other organs, as well as directly from the blood, stools, and urine of patients suffering from the disease. They grow very well upon the ordinary culture-media, such as agar-agar, gelatin, and potato, the temperature of the body being most favorable, but some growth occurs at the ordinary temperature of the room. Upon gelatin and agar there are formed irregularly whitish films, which on close inspection with the lens show a granular appearance. This growth,



Fig. 107.—*Bacillus typhi abdominalis*, from an agar-agar culture six hours old, showing the flagella stained by Löffler's method; $\times 1000$ (Fränkel and Pfeiffer).

however, is not distinctive. Upon acid potato a characteristic transparent pellicle is formed. This may be invisible except to the trained eye, but on scraping the surface with a platinum wire the pellicle can be raised, and on microscopical examination it is found to be composed of bacilli. Sometimes the pellicle is yellowish or brownish. When cultivated in milk there is slight acidity, but coagulation does not occur. When grown in agar containing a little glucose no fermentative gas results. Another feature of importance is the absence of indol reaction, the addition of potassium nitrite and sulphuric acid to bouillon-cultures causing no rose color, such as occurs with some other organisms.

The biological characters of the typhoid bacillus are distinct enough when isolated, but as it occurs so frequently in company with the colon bacillus, whose colonies are similar, numerous technics have been devised for its isolation. These must be studied in books on bacte-

riology. (Compare Cultivation of Typhoid and Colon Bacilli, pages 290 and 296.) One of the most reliable tests for the identification of the typhoid bacillus is the Widal reaction, the clumping of the organism by the blood of typhoid patients, or, better, by the serum of animals immunized against a known culture of the *Bacillus typhosus*. Human typhoid serum may clump colon bacilli also in low dilutions.

Pathogenicity.—Animal experimentation has thus far been unsatisfactory. A few observers have succeeded in producing illness and intestinal lesions by feeding animals with typhoid cultures, particularly after the stomach and intestines have been rendered alkaline with soda and peristalsis has been checked with opium. In most cases injection of the typhoid bacillus has produced septicemic manifestations. The anthropoid apes have been infected by feeding and injection with typhoid bacilli, the resulting intestinal and other lesions bearing a rather distinct similarity to those in man's natural disease. The constant occurrence of the germ, its absence from other conditions, and the absence of any other germ as a constant accompaniment of typhoid fever, have led to the general acceptance of this as the specific cause. Moreover, its properties are such that the spread of the disease in the acknowledged ways is entirely compatible with the acceptance of the bacillus as the specific cause.

Distribution.—The typhoid bacillus occurs both within and without the human body, and doubtless multiplies greatly in the external world when the conditions are favorable. It is found with great regularity in the blood of typhoid patients, especially in the first week of the disease. It occurs in the lesions of the intestines and in the intestinal contents, especially during the second and third weeks of the disease. It is usually less abundant, but often present in the spleen, liver, and kidneys; it may occur in considerable abundance in these organs when there are local complications. It is almost always present in the gall-bladder in cases of typhoid fever, and frequently occasions cholecystitis and not rarely initiates the formation of gall-stones. It also occurs in the lungs, in the parotid gland, and in other organs, and posttyphoidal abscesses may contain the organism in abundance. Complicating lesions of other organs may be dependent solely upon the specific bacillus, it being capable even of acting as a pyogenic organism, or they may be dependent upon secondary or mixed infections.

The typhoid bacillus is peculiarly resistant, and may thrive upon clothing, in soil, and in water for a long time. Cold has no effect, the germ being virulent after freezing and thawing. It has rather more resistance to carbolic acid than other members of the typhocolon group. These features help to explain the spread of the disease and its general prevalence. The organisms are discharged from the body of a patient suffering from the disease mainly in the stools, but in part also in the urine, sweat, and other excreta. If they are not at once destroyed, contamination of clothing, soil, water, etc., may occur, and subsequent infection of susceptible individuals takes place through drinking-water or food with which the infected water or other matters have come in

contact. It is possible that infection may occasionally take place through the lungs by inhalation of dust. This must be very rare. Intra-uterine infection undoubtedly occurs in some instances in which the mother is suffering from typhoid fever.

One means of transmission of typhoid is by means of "carriers." Carriers are persons who after recovery from a typhoid infection harbor somewhere within themselves virulent bacilli without active evidence thereof. They are usually in the gall-bladder, but may be in lymph-nodes or liver. They may be excreted and pollute water or surrounding objects. The reason for this carrying of germs may lie in the fact that their focus is protected from the antibodies of the blood, or they may be "fast" strains.

Pathological Anatomy.—The lesions of typhoid fever are considered with the diseases of the intestines. It is important, however, to add in this place that widespread changes may occur in this disease as a result of the action of the bacillus. Thus there may be focal necroses in the spleen and liver, degenerative changes in the kidneys and muscles, and inflammatory changes in various glandular organs, the periosteum, the bones, or the connective tissues, the result of the direct action of the bacillus. There is a reaction on the part of lymph-adenoid tissue everywhere throughout the body, including all organs, even the larynx, in which definite lymphoid swellings occur in the mucosa, at times leading to ulceration.

Pathological Physiology.—The typhoid bacillus elaborates toxic substances which give rise to fever and other general symptoms as well as to local lesions. Brieger and Fränkel claim to have separated a specific toxalbumin. Whether this be the poison or not, there is no doubt that some form of a toxic body is present, and is endotoxic, not extracellular. During the existence of the disease the system reacts, in some way as yet unknown, to check its progress and to bring it to a termination at the end of four weeks, and lasting immunity is usually conferred. Whether or not there are distinct antitoxic substances remains to be determined.

Protective vaccination with killed typhoid bacilli has been practised. The results of the English and American armies are most encouraging. Both the morbidity and mortality have been reduced. Russel, of the United States Army, concludes that it is a harmless efficient protection against infection and carriers, seldom giving any discomfort, and resulting in an immunity that probably lasts over two years.

Vaccination treatment has been tried during an attack, but with indifferent results. No efficient antiserum has been found.

Agglutination; Gruber-Durham Phenomenon; Widal Reaction.—This reaction is due to the presence, in the serum of inoculated animals or in that of man, of a substance capable of causing massing together and loss of motility of the specific micro-organisms concerned in the infection from which the animal or man furnishing the serum is suffering. This phenomenon may be studied macroscopically or microscopically.

Macroscopically, we speak of a positive reaction when a distinct sediment is seen in the glass containing the culture in a liquid medium, while the rest of the fluid remains clear, whereas before the phenomenon has taken place the whole fluid has had a diffuse cloudiness. Microscopically, we speak of a positive reaction when there occur a clumping and loss of motility of the bacteria, and, at the same time, the control remains free from all massing together. A certain amount of spontaneous clumping often occurs in the controls, but the organisms in the clump still exhibit motility, or there are actively motile individuals at the periphery or a little separated from it. Agglutination has been studied in reference to the bacilli of typhoid fever, plague, cholera, diphtheria, paratyphoid bacilli, the colon bacillus, proteus, and pyocyaneus. In order to obtain agglutination of the diphtheria bacillus it is necessary to immunize an animal highly with the bacteria themselves. The agglutination reaction is considered specific, except in the case of the colon group and proteus. With these two bacilli it is necessary to use the same strain of bacteria with which the animal has been immunized. Agglutination has also been studied with tubercle bacilli, but in this case it is necessary to destroy all the natural clumping of the bacilli by means of shaking with porcelain balls and then filtering.

In studying agglutination with special reference to the Widal reaction, the best results are obtained when one always uses a definite quantity of the culture with a definite quantity of the serum. Cultures grown at temperatures of 25° to 35° C. (77°-95° F.) are better adapted to the reaction than those grown at 37° C. (98.6° F.). The more virulent the culture, the less readily is agglutination obtained. In reference to typhoid bacilli, it is true that a twenty-four-hour culture is the best, since in older cultures pseudo-agglutination shows itself more readily. Widal and Foerster found no difference in the agglutinating properties of typhoid bacilli which had been formalized five months previously from the agglutination seen in fresh cultures. The time that it takes for agglutination to occur is dependent upon the activity of the serum and upon the temperature. At what day after the last injection in the immunization of an animal the agglutination will appear, or at what day after the beginning of the disease in man agglutinin will first show itself, cannot be determined definitely. In men who are ill with typhoid fever the reaction has been demonstrated as early as the third day after the first appearance of the disease, but is often delayed much longer. Agglutinin remains in the blood for varying periods. In children recovering from typhoid fever the average time has been about two months after the convalescence; in adults the average length of time is half a year. In the differentiation between the typhoid and coli bacilli by agglutination a very active serum is necessary. By immunizing an animal with typhoid bacilli we can obtain a serum which will agglutinate both the typhoid bacilli and the colon bacilli, but this occurs in different dilutions. With the typhoid bacilli the dilution may be as high as 1 : 40,000 or 1 : 100,000, while with the coli the highest effective dilution will probably be 1 : 2000. The explanation of this is

that there are group agglutinins which have a certain effect on any one of a group of allied but not identical organisms, and possibly even the specific agglutinins have a certain limited effect (shown when the dilution is not high) on other organisms than those for which they are specific.

In the clinical use of the test the dilution of the serum should be not less than 1 : 50. An active serum will respond very quickly with dilutions of 1 : 100 or more.

Concerning the nature of agglutinin, we note that it probably has a relation with globulin. It can be precipitated by magnesium sulphate. It is destroyed by heating to 70° C. (158° F.). The reaction is regarded by some German authors as being analogous to the phenomenon of coagulation, since the presence of salts is necessary.

This reaction was found in 2283 cases of typhoid fever reported by various writers, and was absent in 109 cases of typhoid fever. It was absent in 1365 non-typhoid cases, and present in 22 non-typhoid patients. It was, therefore, found in 95.5 per cent. of the typhoid cases, and was absent in 98.4 per cent. of the non-typhoid cases; or, taking the entire 3779 cases, the correct result for diagnosis was arrived at in 96.5 per cent. The reaction sometimes persists for some years after the attack of typhoid fever. Sometimes it occurs in cases in which there is typhoid infection without typhoid fever in the ordinary sense. These facts may explain some of the positive results obtained in non-typhoid cases. (See also Immunity.)

Paracolon Infection; Paratyphoid Infection.—This is an acute infection appearing sporadically and in epidemics resembling typhoid fever clinically, but in which the Widal reaction is persistently absent, and in which bacilli closely resembling the typhoid or colon bacilli, though differing in some essential particulars, are isolated from the blood and tissues. The intermediate organisms here referred to differ from the bacillus of typhoid by their ability to produce gas in glucose-containing media, and to produce an alkaline reaction in some media. They differ from the *Bacillus coli communis* by not coagulating milk, not fermenting lactose, and by failing to form indol. The group of intermediates has been divided into a paracolon and a paratyphoid group, according to the closer resemblance to the colon group on the one hand or the typhoid bacillus on the other. The paratyphoids have been divided by Schottmüller into "A" and "B" groups, depending upon the acid reaction in milk. The "A" strains are biologically nearer the bacillus of Eberth, while the "B" organisms are nearer the paracolons. Infections with the "B" paratyphoid bacillus outnumber those with "A." Members of the paracolon group are less closely related—as, for example, in the matter of interagglutination—than those of the paratyphoid group.

The paratyphoids give rise to a milder form of infection than typhoid fever, but the condition is transmissible in the same manner. The diagnosis is to be made by differential agglutinin tests when the bacillus cannot be isolated from the case.

The paracolons are closely allied to the *Bacillus psittacosis* of

Nocard, the *B. icteroides* of Sanarelli, the bacillus of hog-cholera, the *B. enteritidis* of Gärtner¹ (meat-poisoning bacillus), and the *B. dysenteriae* of Shiga. The *B. faecalis alkaligenes* of Petrushki is nearly related and sometimes causes typhoid-like infection, but it does not belong to the group.

Pathological Anatomy.—H. G. Wells and L. O. Scott (1903) summarize the pathological findings in 5 cases of fatal paratyphoid infection, the cases of Strong, Longcope, Sion and Negel, Lucksch, and their own. The most constant change is splenic enlargement, which is in all respects the same as that of typhoid fever or septicemia. The endothelial cells are loaded with pigment evidently the result of hemolysis.

Intestinal Lesions.—In Longcope's and Strong's cases the intestines were quite unaffected; in the other three, ulcerations resembling those of dysentery rather than those of typhoid fever were discovered. Peyer's patches and the solitary follicles were practically unaffected, as were also the mesenteric glands. In no case was there generalized glandular hyperplasia.

In the cases of Longcope and Wells and Scott focal necroses in the liver, differing from those of typhoid in not containing endothelial cells, were found. The changes of proliferation and phagocytosis described by Mallory for typhoid fever were almost entirely absent in the intestinal lesions and very slight in the mesenteric glands, not being more conspicuous than that seen in simple enteritis.

The anatomical picture was that of a septicemia with splenic enlargement and occasionally non-specific ulceration in the intestines. The escape of Peyer's patches suggests an essential if obscure biological difference between the typhoid and paratyphoid organisms.

Nature of Paratyphoid Infection.—The tendency of most pathologists at the present time is to regard paratyphoid infection as distinct in a bacteriological sense rather than in a clinical or general pathological sense, in the same way as pneumonias of varying bacteriology are distinguished only etiologically.

It cannot be denied that there are decided pathological differences, but the practical clinical identity and the near relationship of the bacterial agents warrant the classification of paratyphoid infection as a subvariety of typhoid infection and the rejection of the term "paratyphoid fever" as significant of a separate disease.

BACILLUS COLI COMMUNIS

Synonyms.—*Bacterium coli commune*. It is customary to speak of the "colon group," since it has been recognized that several and perhaps many forms, varying in their ferment action only, have been classed under the name *Bacillus coli communis*. A number of organisms described under different names are probably identical. Among these are *Bacillus neapolitanus* of Emmerich, *B. pyogenes fætidus* of Passet. Several other organisms are either closely allied or identical.

¹ Gärtner's *Bacillus enteritidis* has characters somewhat aberrant from the type here discussed. (See p. 37.)

Morphology.—The *Bacillus coli communis* is an organism almost exactly like the typhoid bacillus in appearance. It is rod shaped, but sometimes elongated and filamentous; at other times (young forms) short and rather rounded—coccus-like. It is motile, and has flagella attached to the periphery of the bacillus. The flagella are shorter, more slender, and less numerous than those of Eberth's bacillus (three to ten in number), and the motility of the organism is less uniform and active. It may be stained by ordinary solutions of anilin dyes, particularly with alkaline or carbolized solutions. It is decolorized by Gram's staining method. The stained bacillus shows light-colored or unstained portions like those of the typhoid bacillus. True spores have not been detected.

Cultivation.—The organism grows luxuriantly upon ordinary media. The most distinctive growth is obtained upon acid potato. An elevated brownish colony is produced, which is usually easily distinguished from the typhoid culture in the same medium. When cultivated in gelatin or agar containing glucose, active gas production results. In liquid media (bouillon) a peculiar odor is developed. Addition of nitrites and pure hydrochloric or sulphuric acid causes a rose-red color—indol reaction. Milk is readily coagulated, partly as a result of acid formation and partly by the elaboration of a coagulating ferment.

Distribution and Pathogenicity.—The colon bacillus is a normal inhabitant of the gastro-intestinal tract. It seems to exercise a beneficial effect in restraining (by its own active growth and acid formation) the growth of putrefactive and possibly pathogenic organisms. In certain inflammatory diseases of the intestines, however, it seems to increase in numbers and doubtless also in virulence. The organism may be found outside the body in various situations, particularly in water.

The *Bacillus coli* is capable of producing inflammatory conditions in different situations. Injected into the peritoneal cavity of animals it gives rise to acute fibrinopurulent peritonitis, and in other parts of the body has analogous effects.

It has been found in various diseases of the gastro-intestinal tract, of the biliary passages, of the urinary system, and of other parts, and is doubtless the direct cause of some of these, as the conditions present are practically the same as those produced by experimental inoculation of pure cultures.

The lesions in the liver may be necrotic, or interstitial or catarrhal inflammation. Colon bacilli are said to precipitate bile-salts. Whether by this means or by inflammatory products, they probably have a part in the production of gall-stones.

Among the gastro-intestinal troubles it has been found in suspicious abundance in various forms of enteritis, in the distended and suppurating appendix, and even in Asiatic cholera. It is known that the strangulation of a knuckle of intestine by a ligature leads to rapid increase of virulence of the contained bacilli. It is possible that in appendicitis and in other intestinal diseases similar conditions lead to increased infectivity, and thus cause an ordinarily harmless organism to become

virulent. In the cases of Asiatic cholera in which this organism has been found the specific germ of cholera has probably been overlooked or has disappeared during the rapid multiplication of the saprophytic *Bacillus coli*.

Peritonitis may result from escape of the bacillus through a ruptured intestine or directly through the wall of the bowel. The latter is particularly prone to occur in cases of strangulation of the intestines.

Various inflammatory diseases of the urinary tract, such as cystitis, pyelitis, and pyelonephritis, are occasioned by this same germ, which first reaches the bladder through the urethra or by penetration of the wall of the bowel and then of the bladder, or, in other cases, infects the kidney primarily, having been carried there by the blood.

Finally, there are cases of peritonitis secondary to enteritis, pleurisy, endocarditis, and other inflammatory diseases, apparently caused by this organism.

Pathological Physiology.—Little is known of the toxic effects of coli infection. Some toxic substance is doubtless produced, which, according to Vaughan, is a highly thermostabile intracellular substance. A reaction similar to the Widal reaction obtained with the typhoid germ has been found to occur when cultures of the colon bacillus are subjected to the action of serum from an animal inoculated with this organism or from a person suffering with appendicitis or other diseases, either due to coli infection or accompanied by such. Occasionally the colon bacilli agglutinate and their motility is checked by typhoid serum. The explanation of this may be that in certain cases of typhoid fever the colon bacillus is also active in the intestines, and in consequence a mixed form of infection is present. In part it is also the result of the presence of group agglutinins that act on different but allied organisms.

There is no antiserum for colon infections, but vaccination treatment has been used with success.

THE DYSENTERY BACILLUS

Certain types of dysentery in the tropics and of acute dysentery of temperate climates are accompanied by bacilli, first recognized by Shiga, and afterward studied by Flexner, Park, Kruse, and others.

The organisms resemble those of the typhoid group, except that they are questionably motile bacilli with few, if any, flagella.

In gelatin culture the colonies resemble those of typhoid bacilli. In bouillon a diffuse cloudiness without production of indol is observed. In glucose bouillon the bacillus does not produce gas or acid. The organisms, as observed by different observers, have differed in some particulars. The original form recognized by Shiga does not ferment mannite, maltose, or saccharose. Some of the later types have been found to ferment mannite and to produce indol, while still others actively ferment mannite and also maltose and saccharose.

The bacillus produces a highly toxic poison, probably of both intra- and extracellular nature. It is resistant up to 70° C. (158° F.), and to

proteolytic ferments. Upon experimental animals the organism has a predilection for the colon. An antiserum has been prepared containing both antitoxic and bactericidal properties. Agglutinins occur during infection.

Bacilli almost identical with the true tropical dysentery bacillus have been found in the summer diarrheas of children. The cases may occur in epidemic or sporadic form. Agglutination tests are used to separate them in the same way that the paratyphoids, typhoids, and paracolons are separated.

The pathological anatomy and physiology of dysentery will be considered in the section on Diseases of the Intestines.

INFLUENZA

Definition.—Influenza is an infectious disease occurring in widespread epidemics and caused by a specific bacillus.

Etiology.—The *Mycobacterium influenzae* was discovered by Pfeiffer and Canon in 1892. The bacilli are extremely small and usually occur singly, though they are occasionally united by the ends, forming short chains. They may be stained with the ordinary anilin dyes, especially with carbol-fuchsin, but are decolorized by Gram's method. The ends of the bacillus are somewhat swollen and usually stain rather more deeply than the shaft. This gives the organism somewhat the appearance of a diplococcus or dumbbell-shaped bacillus. It is not motile. The first generation of the bacilli will grow only in the presence of hemoglobin and are, therefore, cultivated upon glycerin-agar the surface of which has been smeared with rabbit or human blood, forming minute dew-drop-like colonies, seen with difficulty with the naked eye, but clearly with the aid of a lens. The colonies do not coalesce. The appearance of the growth is somewhat like that of condensed moisture on the surface of the culture-medium. Later generations of bacilli may be cultivated on agar or in bouillon.

The bacilli occur abundantly in the sputum of the disease, decreasing in quantity as the case advances. When purulent expectoration ceases the bacillus disappears entirely. Not rarely the organisms are readily recognized in the sputum by simple staining methods. A certain diagnosis is not possible in this way and even in cultures other organisms (see below) have a puzzling resemblance. In fatal cases it has been found in abundance in the tissues of the lung, particularly in cases in which complicating pneumonia has existed. Animal experimentation has thus far been unsatisfactory, though the organism has proved pathogenic for rabbits and monkeys. The symptoms are suggestive of human influenza, but entirely conclusive results have never been obtained. The specific character of the organism is, therefore, inferred rather than demonstrated.

Pathological Anatomy.—There are no specific lesions in this disease. The organisms provoke intense catarrhal processes and, doubtless at times, pneumonia. In some cases the pneumonia of influenza is caused by mixed or secondary infection. Resistant influenzal infec-

tions of the bronchial tubes, with bronchiectasis, constitutes a clinical type of chronic influenza. Inflammatory lesions and hemorrhagic infiltrations in the membranes of the brain and just beneath the membranes have been observed.

A true influenzal meningitis is met in children and can be produced in monkeys. There is an associated bacteremia. Antibody-containing serum can be obtained by injecting the bacilli into goats. This may prove of value in influenzal meningitis, as it has a power of stimulating phagocytosis in the spinal fluid. Bacterins have been used in the treatment of catarrhal influenza. Agglutinins are formed during an attack.

Pathological Physiology.—Very little is known regarding the mode of activity of the bacteria. The constitutional symptoms suggest toxemia, but the nature of the poison is obscure. The immunity from the disease must be exceedingly short, as recurring attacks and relapses may be frequent and succeed one another rapidly. It has been found that the influenza bacillus may remain in the bronchial tubes, especially in tuberculous cases, for months or years. From time to time renewed acute infection takes place. Certain complications and sequels, such as inflammations of the serous surfaces and neuritis, indicate generalized infection and intoxication. The organism does not seem to thrive or multiply in the blood. It has been found in otitis media and other conditions which suggest a metastatic deposit. In general, however, influenza seems to be a local infection with general toxemia, but rarely general infection.

Organisms Resembling the Influenza Bacillus.—A very similar organism, called the pseudo-influenza bacillus, has been described. It is somewhat larger and tends to form long filaments.

The *Koch-Weeks bacillus* of epidemic conjunctivitis differs in its manner of growth and in the fact that hemoglobin is not necessary in the media. It is non-pathogenic in animals. Another influenza-like organism found in conjunctivitis is the *Morax-Axenfeld bacillus* (*Bacillus lacunatus*). This is, however, larger and grows only in the presence of blood or serum, liquefying the latter. These two organisms seem specific for the conjunctiva.

BORDET-GENGOU BACILLUS OF WHOOPING-COUGH

This organism is now accepted as constantly present in cases of pertussis. According to the studies of Wright, it lies between the cilia of the bronchial epithelia, and so interferes with their movements that violent efforts to remove it cause the prolonged coughing attacks. By many authorities, notably the discoverers of the germ, it is looked upon as the cause of the disease, because they can use cultures of it as antigen and fix the complement from the hemolytic series. The organism is a minute ovoid, sporeless, non-motile, poorly staining, Gram-negative rod. It grows aerobically upon media containing glycerin, potato, blood, and agar. The effects are due to an endotoxin. Conditions similar to per-

tussis have been produced in monkeys and dogs by injection and insufflation of cultures. Agglutinins are said to be formed. Bacterins can be used.

BUBONIC PLAGUE

Definition.—The bubonic plague, or pest, is an infectious disease due to a peculiar bacillus, *Bacterium pestis*.

Etiology.—The bacillus of bubonic plague was discovered by Yersin in 1894. In blood drawn from a puncture of the skin and in pus from the affected glands may be found small bacilli somewhat resembling the influenza bacillus. These organisms may be stained readily, and often more deeply at the poles than in the center (Fig. 108). This

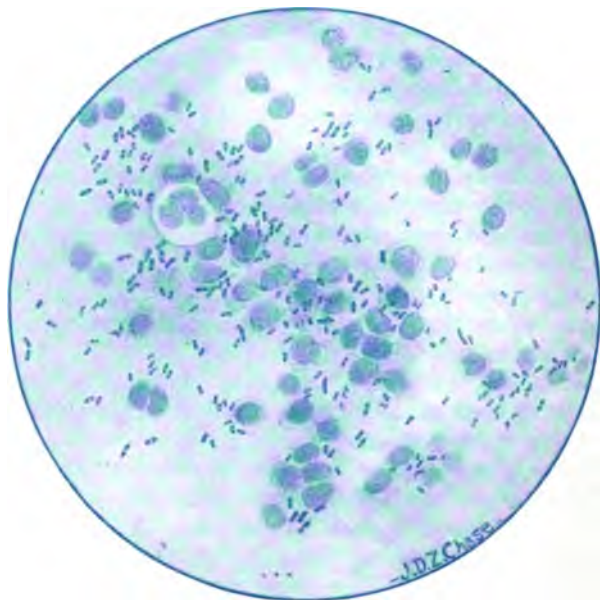


Fig. 108.—Plague or pest bacilli in smear from spleen.

gives them an appearance resembling that of the diplococci, and in specimens from the blood or tissues there is an indistinct capsule. The organism is rather oval in shape, but club-shaped forms are frequent, and in cultures long chains are met with. It is not motile; Gram-negative; it may live in gelatin between 5° and 20° C. (17° and 68° F.) without liquefying the medium. It thrives best in the presence of a high degree of moisture. Pure cultures have been obtained upon various media. Upon glycerin-agar moist, rounded, whitish, or bluish-white colonies are formed. Portions of such colonies removed for examination show the bacilli ranged in chains. The growth in bouillon is very characteristic, as stalactite formations hanging from the surface of the fluid.

Pathogenicity.—The bacillus has been found pathogenic for mice,

rats, guinea-pigs, rabbits, and, indeed, any domestic animal; and the symptoms produced by pure cultures are the same as those induced by inoculating animals with blood or portions of tissue from diseased persons. The lymphatic glands may be swollen and petechial hemorrhage may occur as in the human disease.

Distribution.—In the human being suffering from bubonic plague the bacilli are found in the local lesions of the lymphatic glands, the buboes; and also in the blood and various organs. Yersin showed that flies die of the disease, and succeeded in obtaining the bacillus from their dead bodies. They do not flourish in water, but thrive in milk, butter, and cheese, and these food-stuffs may spread the contagion. The pneumonic form is usually caused by inhalation of dust that has not dried sufficiently long to destroy the bacteria, but is not necessarily due to inhalation of the germs in all cases.

It has been shown that the breath during quiet respiration of plague pneumonia patients does not contain germs, but they are expelled by coughing.

The rat and its fleas are the means of propagation of plague. It has been said that plague is primarily a disease of rats, and that man is only an accidental host. Transmission from animal to animal and animal to man takes place by the rat flea, which will bite man. Bacilli, existing in the saliva and digestive tract, may easily be deposited upon the surface of an animal or man and rubbed into any small wound of the skin, such, for instance, as may be made by the flea-bite. Bacilli may also be deposited by fleas or rats upon food or household utensils.

Not only rats but most rodents are susceptible to plague. Ground squirrels of California have been found extensively affected, and the marmot of Tibet is a constant source of infection in that country.

It is said that mild, unrecognized cases may act as "carriers."

Pathological Anatomy.—There are three forms of plague according to the chief clinical and anatomical manifestations: the bubonic, pneumonic, and septicemic. The organism produces swelling and suppuration of lymphatic glands, particularly those of the groin, and, secondarily, lesions of internal organs. The lymphatic glands swell quickly, become tender and congested, and then soften, forming a rather thick pus. This is sometimes blood tinged. Histologically, the exudate is chiefly large mononuclears, actively phagocytic of the very numerous pest bacilli. This form of exudate soon gives way to necrosis and spread of bacilli outward. Petechial hemorrhages and blood-stained effusions into the serous cavities may occur. Petechiæ of the skin are apt to develop as a result of slight traumatisms. Thus, the bite of an insect, instead of producing its usual results, may cause distinct ecchymoses in persons suffering from the disease. The pulmonary form produces a bloody edematous form of pneumonia; fibrin appears relatively late. This may be quite independent of glandular enlargements externally. A "septicemic form" is characterized by general infection with widespread involvement of the lymphatic glands, but without distinct buboes. Areas of necrosis take the place of pest abscesses.

Pathological Physiology.—It seems that the distribution of the bacillus in the blood, as well as toxic substances, chiefly endotoxic, contribute to the general disturbance of health. By successive inoculation immunity has been produced, and antitoxic sera have thus been obtained. The serum has been used in man with considerable success as a protective and also a curative agent. It often fails in advanced cases.

Haffkine used his method of inoculation as in cholera and obtained encouraging results.

SOFT CHANCRE

Definition.—The soft chancre or chancroid is an infectious venereal sore appearing upon the external genitalia. The bacillus of Ducrey is said to be the specific organism.

Etiology.—The soft chancre occurs almost exclusively upon the genital organs or the surrounding parts. It is always caused by direct contagion.

The bacillus of Ducrey and Unna is a rod-shaped organism about $1.8\ \mu$ in length and $0.5\ \mu$ in thickness, and appears somewhat compressed in the middle, so that it has a figure-of-8 shape. The ends are rounded and the organisms often occur in chains, or later in the disease in pairs, as a diplobacillus.

The demonstration of the bacillus in the pus is comparatively easy. The specimen is stained with alkaline solutions of methylene-blue and quickly decolorized with weak acetic acid solution. It may be well stained with carbol-fuchsin, alcohol being used to decolorize. It is Gram-negative. In the tissues the demonstration is more difficult.

Growth is most luxuriant in a medium of fresh blood and bouillon, but unmixed human blood is the best medium for obtaining cultures from a source open to contamination, the fresh blood apparently inhibiting to a certain extent the growth of extraneous organisms. The best solid medium consists of 2 parts of alkaline agar and 1 part of fresh rabbit's blood if seeded with material obtained by aspiration of a bubo. Cultures on ordinary media have thus far been unsuccessful.

The bacillus is found in the pus of the soft chancre, as well as in the deeper parts, lying between the cells and frequently within the leukocytes. It has also been discovered in the pus and walls of ulcerating buboes, but is generally absent in the pus of unopened buboes.

Mixed Infection.—Various other organisms have been found associated with the bacillus, including streptococci, staphylococci, the gonococcus, and bacilli of uncertain nature.

Pathological Anatomy.—The soft chancre is an ulcer of variable character. Usually it is a simple ulcer, with suppurating base and edges, not differing from ulcers due to other causes. Sometimes the ulceration seems more malignant and takes on a phagedenic or serpiginous character (see Ulceration). The neighboring lymphatic glands are usually enlarged and sometimes undergo suppurative softening (bubo).

Pathological Physiology.—Little is known of the existence of special toxic bodies in this disease. It is believed, however, by some that toxins are produced by the bacilli, and that these are capable of producing secondary lesions (bubo) without the presence of the bacilli themselves.

MALTA FEVER

Synonyms.—Mediterranean Fever; Gibraltar Fever; Febris Undulans.

Definition.—This disease has been described as a form of irregular fever occurring along the Mediterranean coasts. It was formerly regarded as an aberrant form of typhoid fever, but is certainly independent.

Etiology.—The micro-organism discovered by Bruce, and designated *Micrococcus melitensis*, is by many regarded as the specific cause. This is an oval micrococcus about $\frac{1}{2} \mu$ in diameter, occurring singly or in pairs, and in cultures as short chains. By Babes it is regarded as a bacillus, and certainly agglutinates with more readiness than cocci are wont to do. It has no motility of its own. It may be stained with ordinary solutions of anilin dyes, but not by Gram's method. It occurs abundantly in the spleen, and is occasionally found in the blood by blood-cultures. Pure cultures have been obtained, and inoculation in monkeys has seemed to give positive results. Malta fever is not contagious. The micro-organisms seem to enter the body through the respiratory or the intestinal tract. Agglutination occurs readily with patients' serum, and may be used in diagnosis. The organism is excreted in urine and milk. The goat, which is used largely for milk supply in Malta, may carry the germs and excrete them without being actively infected with the disease.

Pathological Anatomy.—The mucous membrane of the small intestine is red and the solitary follicles and Peyer's patches are sometimes swollen. The mucosa of the large intestine is generally dark red and presents small round or larger irregular ulcerations, from which intestinal hemorrhages occur. In some cases lesions of the ileum resembling those of typhoid fever have been described; but it is doubtful if the cases in which these occurred were Malta fever. The spleen is enlarged and hyperemic.

Pathological Physiology.—Malta fever is characterized by irregular febrile movements. The cause of this irregularity and the nature of the toxic substance generated in the disease are unknown.

RHINOSCLEROMA

This is a disease affecting the skin about the anterior nares and adjacent parts, and probably caused by a specific bacillus. The disease has been especially observed in central Europe. It presents itself in the form of nodular thickening of the skin of the nose and lip, and sometimes spreads to the neighboring mucous membranes—mouth,

pharynx, or larynx. In the latter situations ulceration of the surface is frequent; the lesions of the skin rarely ulcerate. Histologically, the growth consists of round granulation tissue cells. Frequently the cells suffer hyaline degeneration, forming rounded hyaline bodies, with small granular nuclear masses. These are called Mikulicz cells. The bacilli may be found between the cells and within them, especially such as present hyaline degeneration. The micro-organism resembles the bacillus of Friedländer, but by some is said to be Gram-positive. This is denied by others. When cultivated upon blood-serum or agar it retains its capsule. Inoculation experiments have thus far failed to produce the disease in animals. The etiological relationship of the so-called *Bacterium rhinoscleromatis* is doubted by many observers. It is very close to Friedländer's pneumobacillus, but does not form gas in sugar media.

GLANDERS

Definition.—Glanders is an infectious and contagious disease of horses and asses, sometimes communicated to other animals and to man, and caused by a specific bacillus.

Etiology.—The *Mycobacterium mallei* was first isolated by Löffler and Schütz. It is an organism resembling the tubercle bacillus, though somewhat shorter and thicker. In cultures it may grow to long filaments and not rarely it breaks up into coccus-like fragments. It occurs in the lesions of the disease singly or in clumps, and has been found in the blood. The bacillus is non-motile and does not possess flagella. Stained specimens show parts that do not receive the stain. These have been regarded as spores, but are more generally thought to be areas of degeneration. Ordinary solutions of anilin dyes, and especially alkaline solutions, stain the organism very well. The demonstration of the bacillus in the tissues requires prolonged staining and rapid decolorization. It is Gram-negative.

Cultivation.—Cultures are best obtained from softened nodules of guinea-pigs inoculated with infected pus, or from the testicles after injection of infective matter into the peritoneal cavity. The organism grows quite readily upon ordinary media, but the most characteristic culture is seen upon boiled potato. The colony first appears as a honey-like layer, which becomes brownish in color. The potato itself becomes greenish brown beneath and around the colony. The cultivation is most successful between 30° and 40° C. (86° and 104° F.).

Drying and elevated temperatures rapidly destroy the organism, and germicides kill it quite readily. The bacillus is a pure parasite, multiplying only in the body of infected animals or man.

Pathogenicity.—The specific character of the bacillus is unquestionable. Inoculation of guinea-pigs, rabbits, field-mice, or other animals with infected pus or with pure cultures leads to nodular lesions at the point of introduction, with subsequent softening and ulceration. Secondly, the lymphatic glands enlarge and after from two to four weeks suppurate. In male guinea-pigs a practically pathognomonic

condition (great enlargement of the testicles) is observed within two or three days after intraperitoneal inoculation with pure cultures or exudate from the lesions of the disease. After death nodules are found in the liver, spleen, kidneys, or other organs, and these contain the bacilli. In horses and asses characteristic lesions of the mucous membranes have been produced experimentally; while in man accidental infection of hostlers or others coming in contact with diseased animals, and of bacteriologists working with cultures, have been repeatedly observed. In one case in our own knowledge a man was infected in a stable in which a glandered horse was kept, and the bacteriologist who isolated the organisms from the patient accidentally infected himself with the cultures. The spontaneous infection occurs through some abrasion or wound.

There are two fairly distinct forms of glanders, the acute and chronic. The former is septicemic with abscesses, both widely scattered in the organs and in the lymphatics of the skin (farcy buds). The term *farcy* is given to the form with subcutaneous abscesses, usually an acute condition in man, but commonly more chronic in horses. The chronic form is slow of progression, chiefly attacking the lymphatic organs, and showing slowly progressive lesions either local or general.

Pathological Anatomy.—In horses glanders presents characteristic lesions of the mucosa of the nose. At first there are found slightly elevated nodules, which have a marked tendency to soften, forming irregular ulcerations that become confluent. The floor and edges of the ulcers are yellowish and necrotic in appearance, and discharge more or less purulent matter. The lymphatic glands of the neck and elsewhere enlarge and may suppurate. In the skin the lesions are much the same, but more sluggish. Nodules are not rarely met with in the lungs. These are grayish or pinkish in color, and tend to rapid necrosis. More rarely nodules or ulcers are found in the mucosa of the gastro-intestinal tract.

In man similar nodules and ulcerations may be found in the nose, larynx, or trachea; and external lesions resembling small or large carbuncles are found.

Histologically, the lesions of glanders consist of aggregations of round cells of lymphoid or polymorphonuclear type surrounded by a zone of spindle and epithelioid cells. Some of the latter swell, and their nucleus divides by direct division, causing a kind of giant cell. There is a marked tendency to suppurative or necrotic softening, and sometimes hemorrhagic infiltration may be pronounced.

Pathological Physiology.—A toxic substance called *mallein* (a bacterial protein) has been obtained from cultures of the bacilli. Injected into infected animals this acts somewhat as does tuberculin in tuberculosis. A special toxin is probably active in the production of the general symptoms of the disease. By repeated dosage with mallein it is claimed that immunity may be conferred. The poison of *Mycobacterium mallei* is endotoxic. Agglutinins are produced during an attack, and a complement-fixing body can be discovered in most cases.

TETANUS

Definition.—Tetanus is an acute infectious disease due to a specific bacillus, the *Bacillus tetani*, discovered by Nicolaier and isolated by Kitasato.

Etiology.—The bacilli occur in the form of cylindrical rods, which are frequently swollen at one end, due to the presence of a rounded spore (Fig. 109). They are slightly motile in the vegetative state, being supplied with peritrichous flagella; in the spore stage they are non-motile. They usually occur singly, though occasionally a few may be seen end to end. They occur in the local lesions from which traumatic tetanus takes its origin, and may sometimes be readily demonstrated by spreading some of the pus or exudate upon a cover-glass and staining with the ordinary anilin stains. They also stain by Gram's method. The bacillus does not diffuse itself through the body, but in a few cases



Fig. 109.—*Bacillus tetani*; $\times 1000$ (Fränkel and Pfeiffer).

it has been found in the central nervous system. The organism is readily destroyed by heat, but its spores are quite resistant.

Cultivation of the tetanus bacillus is difficult. It is obtained from garden-earth or the pus of infected wounds by submitting the material to sufficient heat to destroy other organisms, even the bacillus of tetanus itself, leaving the spores uninjured. With this material animals are inoculated, and from the products of the local lesions or directly from the original material cultures are made in gelatin.

The organism is strictly anaërobic. The typical culture is obtained in the depth of gelatin. Deep beneath the surface there are formed along the line of puncture pointed processes standing out at right angles from the puncture. After a week liquefaction of the gelatin occurs, and an accumulation containing grayish-white turbid liquid is formed. When the growth is formed on the surface of gelatin in an atmosphere of hydrogen a similar radiating structure is found in the colonies, the cen-

ters of which are rather dense. Liquefaction of the gelatin subsequently takes place. Considerable gas with a pungent odor is produced in the growth of this bacillus.

Distribution.—The tetanus bacillus is found very frequently in garden-earth, in the intestinal discharges of animals, and upon various articles about stables. Infection occurs in human beings or animals through punctures made by nails, splinters, and the like.

Pathogenicity.—The bacillus placed upon an open wound may not give rise to the disease, from the fact that the presence of oxygen prevents its growth. Subcutaneous inoculation, however, causes rapid destruction of animals with typical symptoms. The period of incubation may be only a few hours, or one or two days, or it may be several weeks. The association of certain other organisms, such as the pus-producing organisms, seems to favor the development of the disease by preventing phagocytic action of leukocytes, or by consuming oxygen and thus allowing the tetanus bacillus to flourish.

The toxin is manufactured *in loco* and taken up by the nervous tissue, for which it has a predilection.

Pathological Anatomy.—No characteristic lesions are found in this disease. Locally, a wound or injury through which inoculation has taken place may be discovered; but this is only exceptionally extensive. Sometimes no local injury can be discovered, and it is supposed that infection at times occurs through the gastro-intestinal tract or through other mucous membranes. Intense congestion of parts of the nervous system and granular degeneration of the anterior spinal motor cells may be found at the autopsy, but these are not characteristic.

Pathological Physiology.—Two distinct toxins have been recognized—*tetanospasmin*, which is the predominant poison and that which causes the spasms, and *tetanolysin*, a hemolytic substance of uncertain importance. The toxin of tetanus is almost inconceivably poisonous, a fact which accounts for the development of a fatal disease in cases in which the number of bacilli is minimal.

The spasmodic seizures first affect the muscles near the point of inoculation and in mild infections may be confined to these muscles. This has been explained by the experiments of Meyer and Ransom and others, who showed that the toxin reaches the nerve-cells of the spinal cord by traveling from the muscular end-plates of the motor nerves through the axis-cylinders to the cord. The toxin injected into the blood does not pass directly to the nerve-centers, but always travels up the motor nerves as described. The parts first affected by spasm are, therefore, those about the point of inoculation and of elaboration of the toxin.

Tetanus antitoxin has been obtained by successive inoculations of animals with the toxin, and in laboratory experiments has been found specific and exact in its antagonism to the toxin. In treating the disease in man or animals the results have been disappointing, but this is now known to be due to the manner in which the toxin and antitoxin are respectively distributed and absorbed, and to the fact that the toxin

has usually reached the vulnerable nerve-centers, and been tightly anchored in them, at the time when the antitoxin is injected. The antitoxin must be first absorbed by the lymphatics and carried to the blood, with which it is distributed to the fluids of the body, whence it is again absorbed by the nerves. It is not taken up directly from the blood by either the central or peripheral nervous tissue. For these reasons the subcutaneous injection of antitoxin fails to effect the neutralization of much of the toxin, since the latter is quickly absorbed by the peripheral nerves. Intravenous, intraneural, and subdural (spinal) injections are more rapid in their effects and, therefore, preferred. To prevent combination of toxin and nervous tissue antitoxin must be introduced before symptoms arise. It is, therefore, more useful as a preventive than as a curative.

ANTHRAX

Definition.—Anthrax is a specific infection due to a characteristic bacillus. It occurs most frequently in cows and sheep; it may affect other animals and man. Dogs, cats, birds, and cold-blooded animals are quite immune. In animals it is called splenic fever; in man, malignant pustule and wool-sorters' disease.

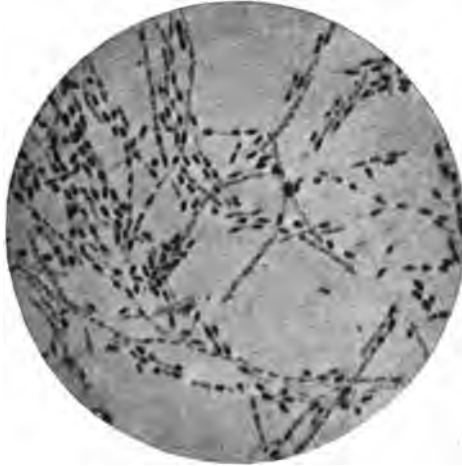


Fig. 110.—*Bacterium anthracis*, stained to show the spores (Fränkel and Pfeiffer).

Etiology.—The *Bacterium anthracis* was first observed by Pollender in 1849, and shown to be the specific cause of anthrax by Davaine in 1863. In 1879 Koch, Pasteur, and others succeeded in making pure cultures and in demonstrating their pathogenicity. It was, therefore, the first pathogenic organism definitely isolated. The anthrax bacillus is a non-motile rod-shaped organism that has a decided tendency to form long chains. The individual bacillus is from 5 to 20 μ in length and from 1 to 1.25 μ in thickness. The chains appear as threads often with a little thickening at the ends of the individual bacilli showing the points of contact. The ends are squared or slightly concave. In artificial cul-

tures in the presence of oxygen spores are formed within the bacilli. These are elliptical or oval in shape, and do not alter the configuration of the bacillus (Fig. 110).

The organism is easily stained with the simple anilin dyes, and may be demonstrated in the blood or the tissues by Gram's or Weigert's stains. There are no flagella.

Cultivation.—The anthrax bacillus may be obtained in pure culture from the diseased organs upon various media. The culture in gelatin is most characteristic. Upon plates there are formed whitish colonies, which under low powers of the microscope show a tufted, irregular character at the edges and upon the surface, suggesting bunches of twisted wool-fibers. The gelatin is slightly liquefied. The tufts may be removed by pressing a cover-glass against the surface of the colony, and when stained are found to consist of curved parallel chains of bacilli. In puncture-cultures filaments project at right angles to the puncture toward the sides of the test-tube, and the growth at the surface, where oxygen is abundant, is luxuriant, while that in the depth is comparatively sparse.

Pathogenicity.—The infectiveness of the bacillus is undoubted. A small portion introduced into a susceptible animal gives rise to marked symptoms in twelve or twenty-four hours, and death soon follows. The bacilli may be demonstrated in the blood and in various organs in great abundance. When the bacillus is killed and the spores are introduced into the body similar results follow. The spores are highly resistant and may preserve their virulence for years. Sporeless varieties of anthrax bacilli have been encountered and have been produced by cultivation under unfavorable conditions.

Distribution.—The anthrax bacillus occurs in all of the local lesions, and from these is carried into the blood and the organs, particularly the spleen, liver, kidneys, and lungs, where it is found in the capillaries in immense numbers. The structure of these organs is, as a rule, little affected, probably because death occurs before changes can take place. The organisms may be present in only small numbers in the blood of the general circulation when the capillaries of the various organs are filled with them. The organisms are discharged from the body in the stools, urine, and other discharges, and are thus conveyed to other animals. At one time it was supposed that they were scattered about by earth-worms obtaining them from cadavers; this is scarcely probable. Multiplication of the organisms outside the body does not occur to any extent, but the organisms, and particularly the spores, may live a long time, and may be conveyed to great distances in infected materials, particularly wool, hides, bristles, and the like.

Mode of Infection.—In animals infection most frequently occurs through the gastro-intestinal tract, the bacilli being swallowed with fodder that has been contaminated. The organisms may, however, gain entrance through the lungs or through external abrasions. The latter form of infection is most common in man, though gastro-intestinal and pulmonary infection sometimes occur.

Pathological Anatomy.—The lesions produced by anthrax are more or less local, but occasionally are septicemic. In man, after infection of the skin through abrasions in persons handling the hides or wool or other materials from diseased animals, a swelling of greater or less size develops. This is intensely inflammatory, often covered and surrounded by slight bullous vesicles, and attended with considerable edema. Erosion of the surface may take place and sanious liquid may be discharged, with the formation of crusts. Histologically, the process consists of rapid infiltration of the corium and papillary bodies with leukocytes. The bacilli are found in abundance between the cells, and hemorrhagic infiltration and serosanguinolent edema are observed. Necrosis subsequently occurs, though not to a considerable extent. When infection takes place through the gastro-intestinal tract, as is sometimes observed in man and very commonly in animals, lesions somewhat like the above are formed in the mucosa and submucosa of the small intestine, less frequently of other parts. At first these lesions appear as hemorrhagic extravasations, then swelling follows, and finally the surface ulcerates, leaving irregular excavations with blood-stained bases and edges. Profuse diarrhea with bloody discharges may occur. Infection through the lungs occurs in men engaged in handling infected wool (wool-sorters' disease), and in persons working in paper factories, where infected rags carry the germs. In these instances the bacilli lodge in the alveoli of the lungs, causing rapid cellular exudation with considerable edema and hemorrhagic infiltration. The process is lobular in character, but large areas of the lungs may be simultaneously involved. Serosanguinolent pleurisy, swelling of the lymphatic glands of the mediastinum, and hemorrhagic extravasations of the mediastinum are not unusual. In all forms there is acute inflammatory or hemorrhagic swelling of the spleen.

Pathological Physiology.—The presence of the anthrax bacillus probably leads to the formation of toxic materials in the blood, although while a poisonous albumose has been obtained from cultures, its nature is not understood and its identity doubted by some. The general symptoms, however, are probably in large measure the result of dissemination of the bacilli themselves and their local effects.

Their action seems to be directed primarily against the circulatory system, as the toxin calls forth leakage of serum and escape of blood. Much fibrin is formed, but there is little tendency to cellular accumulation or suppuration.

It has been found possible by cultivation at high temperatures, by introducing the organisms into insusceptible animals, and also by adding chemical agents to cultures to alter the pathogenicity of the bacillus to such an extent as to make it harmless, even to white mice. By introduction of such cultures and subsequent successive inoculation with cultures of increasing virulence protection has been afforded. Antitoxic substances have been obtained from the blood of protected animals, but the method of successive vaccinations rather than the use of antitoxic serum is at present relied upon to combat the disease.

MALIGNANT EDEMA

Definition.—Malignant edema is a form of intense infective inflammation and necrosis observed in certain animals and in man, and is due to a specific micro-organism. The condition has frequently been described by clinicians as gaseous gangrene, traumatic gangrene, gangrene foudroyante, etc. Infectious emphysema (*q. v.*) has doubtless often been mistaken for this disease.

Etiology.—The micro-organism of malignant edema was described by Pasteur and named the *Vibrio septicus*. Koch showed that it does not flourish in the blood, and that the name given by Pasteur is, therefore, not appropriate. He, therefore, named it *Bacillus œdematis maligni*. This organism is widely distributed. It is very commonly present in the soil, particularly in garden-earth, and is often found in dust and in the intestinal contents of animals. Introduced into the subcutaneous tissue of animals it multiplies greatly and sets up a violent local process. The bacilli are readily obtained from the diseased area, and may be stained with the ordinary anilin dyes, but not by Gram's method. The bacillus resembles the anthrax bacillus very closely, but is somewhat more slender. It is prone to occur in pairs or in chains or long filaments, the several bacilli being joined end to end. Movement of the organisms is frequently observed, and lateral flagella are found by appropriate stains. In the spore formation the center of the organism swells and the spore is developed within.

The cultivation of this organism is generally easy. White mice or other susceptible animals are first infected by introducing powdered garden-earth into a subcutaneous sac. Direct infection of an open wound will not succeed, as the organism is strictly anaërobic.

From the pus in the subcutaneous tissues growths may be obtained upon the surface of gelatin in an atmosphere of hydrogen, or in puncture-cultures in gelatin from which oxygen has been excluded. On the surface of the gelatin are formed small grayish-white bodies, which increase in size with advancing age. Portions removed from these and stained show masses of bacilli in the form of long filaments. In the gelatin-tube there are formed whitish spherical colonies of a somewhat cloudy appearance. These consist of a turbid liquid, the gelatin undergoing liquefaction. There is also some gas production, the gas formed having a peculiar and unpleasant odor. This is marked when the medium contains glucose (Fig. 111).

Distribution.—The bacillus of malignant edema occurs only in the subcutaneous tissues near the point of inoculation, in the muscles, and



Fig. 111.—Bacillus of malignant edema growing in glucose-gelatin (Fränkel and Pfeiffer).

in the peritoneal cavity at the time of death. It does not invade the blood, as the amount of oxygen there present prevents its growth, and it flourishes in the subcutaneous tissue because this is least accessible to oxygen. In bodies dead some time the organism may spread to the blood and the organs of the body. The distribution of the organisms outside the body has been referred to.

Pathogenicity.—The bacillus of malignant edema is undoubtedly the cause of the disease in question, as has been proved by inoculations upon mice, guinea-pigs, and other animals. Cats and dogs are less susceptible than other animals; cattle seem to be almost wholly immune.

Pathological Anatomy.—The lesions of malignant edema consist of various forms of rapid suppuration and necrotic inflammation of the subcutaneous tissues. These may rapidly form emphysematous and gangrenous alterations of the subcutaneous tissues, with sometimes pus formation, at other times extensive hemorrhagic infiltration.

Pathological Physiology.—Toxins are doubtless formed, but these have not as yet received special attention. Artificial immunity has been secured by injections of sterilized cultures of the bacillus in bouillon, and by other methods. A few cases of malignant edema have been reported in man, some following injection of musk in the course of typhoid fever, some occurring in the puerperium, and some apparently without external injury. Infection in the latter probably occurred from the mucous surfaces. In all cases the general vitality of the patient was reduced by some previous disease.

INFECTIOUS EMPHYSEMA

Definition.—This term is provisionally applied to a form of infection that has been described under various names, such as gaseous gangrene, gas phlegmon, emphysematous necrosis, and the like. Undoubtedly it has been mistaken for malignant edema in certain cases. The disease is caused by the *Bacillus aërogenes capsulatus* of Welch and Nuttall.

Etiology.—The bacillus in question is a non-motile organism of variable size, 3 to 6 μ in length, and about the thickness of an anthrax bacillus, with adjacent ends slightly rounded or square cut, and occurring singly, in pairs, clumps, or sometimes in short chains. Very rarely it occurs in long threads. It is easily stained with the ordinary anilin dyes or Gram's stain. A capsule is sometimes demonstrable in specimens obtained from the body or from agar-cultures. The bacillus does not form spores. It is probably identical with the *Bacillus phlegmones emphysematosæ* of Fränkel.

Cultivation.—The organism is anaërobic, no growth occurring on the surface of solid media in the presence of oxygen. In media containing fermentable material gas formation is regularly observed. The colonies in agar are grayish-white or slightly brownish; those in the depth appearing as small spheres or ovals slightly flattened, with knob-

like or feathery projections. The cultures in gelatin show slight and slowly developing liquefaction.

Pathogenicity.—By experiments on animals exactly the same lesions are produced as those found in man.

Pathological Anatomy.—The lesions of this infection are widespread. At the point of inoculation there may be found edematous infiltration, with blood-stained fluid, and emphysema due to gas formation. Rapid necrosis or gangrenous softening of the tissue may occur. The entire surface of the body sometimes becomes emphysematous, and at the autopsy the organs, especially the myocardium, kidneys, liver, and spleen, present a characteristic appearance. They are lighter in color, and on inspection are found to be filled with minute vacuoles or gas-bubbles. The blood of the heart and vessels presents a foamy condition, due to the gas formation. Practically, any of the tissues of the body may be affected. Microscopically, the occurrence of gas-vesicles with numerous bacilli in their walls is the most striking feature.

Regarding the mode of infection, it seems likely that in all cases the organisms enter through some injury or abrasion connected with the external world. Some cases have followed traumatic injuries, others occur in connection with disease marked by ulcerations of the surface of mucous membranes, and at least one instance has been carefully studied in which the disease occurred during the puerperium, probably due to uterine infection. It is not improbable that some of the cases of supposed air-embolism from douching of the uterus after labor are, in reality, cases of this form of infection.

Other bacteria, notably *Bacterium mucosus capsulatus*, *B. coli*, and *B. perfringens*, have been found in gaseous edema, or as gas producers in inflammatory exudates.

TUBERCULOSIS

Definition.—The term “tuberculosis” refers to various conditions due to infection with the tubercle bacillus, *Mycobacterium tuberculosis*, no matter what the form or individual peculiarities of the case. The name was originally employed because of the occurrence of small nodules or “tubercles.” It must be remembered, however, that other diseases show small miliary nodules, perhaps indistinguishable to the naked eye from miliary tubercles, and that tuberculosis sometimes occurs without a single definite tubercle.¹

Etiology.—Tuberculosis is infectious and contagious, the bacilli being transferred by the secretions and excretions from diseased persons to a susceptible individual through the air, food, drink, or in other ways. The infectious character of the disease was long suspected, but was definitely proved by Villemin in 1865, and in 1882 Koch succeeded in isolating the infective bacillus. Predisposing causes are of some importance. Formerly family susceptibility was thought an all-

¹ In this book the adjective “tuberculous” applies to the specific disease caused by the bacillus of Koch, other conditions being called “tubercular.”

important cause, and the disease was supposed to be transmitted directly in families. At the present time we recognize the transmission of susceptibility, and very rarely transmission of the disease itself, from parent to child. Warthin has found many cases in literature and his own observation where direct transplacental passage of tubercle bacilli has occurred, both with or without lesions in the placenta. Tubercle bacilli have been found in the semen. (See Placenta.) Susceptible persons frequently show delicate organization with poor development of the body, particularly of the chest. When this susceptibility or predisposition exists, there is naturally greater receptivity for bacilli spread around by tuberculous associates. Besides inherited suscepti-

bility, acquired predisposition may result from occupations which lower vitality, from grief, prolonged nervous strain, and exhaustion; and some one of the organs may be specially predisposed by injuries, as in cases of tuberculosis occurring in the lungs of those inhaling sharp particles of metal, coal, and the like. Such mechanical lesions prepare a place of lesser resistance, and tubercle bacilli more easily gain a footing than in normal tissues. Continued local anemia seems to predispose.

Fig. 112.—Tubercle bacilli in the sputum; Zeiss's homog. immersion $\frac{1}{2}$, Oc. 4; magnified about 1000 diam.

The *human tubercle bacillus* is a rod-shaped organism, 1.5 to 3.5 μ in length and from 0.2 to 0.5 μ in breadth. Sometimes it is even longer, especially after cultivation. It often occurs in pairs or in groups arranged end to end, but not overlapping, and evidently not attached the one to the other. It also occurs either straight or more or less curved, and may often be found S-shaped or in branching forms. When stained, it may either appear uniformly colored or may present a beaded appearance, regarded by some as due to spores, a view that has not been proved. The condition is caused by the alternation of portions well stained and intervening parts with little or no stain (Fig. 112). These light areas, formerly regarded as spores (Koch), are now believed to be the result of fragmentation of the bacillus and retraction of the substance of the organism causing vacant areas. In other words, the light areas are due to degeneration. They are certainly not spores. There appears to be a narrow capsule closely applied to the organism, and the capsule seems to contain in especial abundance the wax-like substance that occasions the peculiar acid-fast staining properties of the bacillus. The bacillus is non-motile and does not have flagella. It is, therefore, transported by outside agencies entirely.

The tubercle bacilli found in man, cattle, and fowl exhibit structural and cultural differences, though they are probably the same

bacilli exhibiting different characteristics caused by their growth in different environments.

The *bovine bacillus* is much shorter and thicker than the human bacillus, being from 1.5 to 2 μ in length and of an oval shape, the length being not more than double the breadth. It is straight, and does not exhibit the curved and branching forms of the human bacilli. When stained, it is more uniformly colored, the beading being usually absent. Cultures of the bovine organism in glycerin broth are at first acid, but become alkaline, while those of the human species never become alkaline.

Tuberculin made from the bovine species is alkaline; that from the human species is highly acid.

The human type is more easily grown. The bovine type will infect rabbits uniformly, while great quantities of human culture are necessary. Human bacilli will not infect calves with progressive lesions.



Fig. 113.—Culture of tubercle bacilli on glycerin-agar, four weeks old (Fränkel and Pfeiffer).



Fig. 114.—*Bacillus tuberculosis*; adhesive cover-glass preparation from a fourteen-day-old blood-serum culture; $\times 100$ (Fränkel and Pfeiffer).

The *avian tubercle bacillus* differs from the human bacillus in that it is more often club shaped and branching, and that it grows more luxuriantly upon glycerin-agar and blood-serum, and at a much higher temperature—45° C. (113° F.). It will also grow on ordinary agar, but not on potato. It is much more resistant to heat, especially as regards its virulence. It will not infect guinea-pigs with a progressive lesion.

Artificial culture of the *Mycobacterium tuberculosis* was first successfully accomplished by the use of blood-serum as a medium. The bacillus grows very slowly; after ten days or two weeks the surface of the medium shows dry flakish deposits, somewhat resembling the scales in certain

skin diseases (Fig. 113). The edges of these flakes tend to elevate themselves a little, and the substance of the growth has a crumbled appearance. Placed under a cover-glass in mass and examined with the microscope these flakes are found to be composed of contorted masses of bacilli (Fig. 114). Pure cultures are best obtained from the lymphatic glands of animals artificially infected and destroyed before the tuberculous foci have advanced to the stage of necrotic change. Cultures may be obtained with some difficulty from the sputum or other excreta. At the present time blood-serum is less frequently used, as it has been found that agar-agar slightly acidulated and containing a large proportion of glycerin, and bouillon containing glycerin, serve as useful media. The original culture is still, as a rule, obtained in blood-serum or coagulated egg. Even potato and other simple substances are found to be satisfactory media. The bacillus requires a rather even temperature for its growth: it flourishes best at 37.5° C. (99.5° F.), and does not grow below 29° C. (84° F.) or above 42° C. (107.6° F.). Exposure to higher temperatures (75° C.; 167° F.) rapidly destroys it, and strong sunlight is destructive. It requires considerable air and always grows upon the surface of the medium in which it is cultivated. Prolonged cultivation upon artificial media lessens its virulence.

The **demonstration** of the tubercle bacillus by staining methods is extremely easy and satisfactory. It has been found that this organism, like that of lepra and the smegma bacillus, does not readily stain, but after receiving a stain retains it despite the action of strong mineral acids. Upon this principle the methods of staining are based. Koch used as a stain a gentian-violet solution containing anilin oil, the latter playing the part of a mordant or an agent to fix the stain in resistant bacilli. The specimen was then decolorized by treating it with a solution of a mineral acid, which removes the stain from everything but the tubercle bacillus. A counterstain might then be used to render the detection of the bacilli more easy.

The most convenient method is the following: Sputum is spread in a film upon thin cover-glasses or slides. These are allowed to dry in air and then thoroughly fixed by drawing the specimen through a Bunsen flame three times; a drop or two of Ziehl's solution of carbolfuchsin are added and heated until the liquid steams. After two or three minutes the stain is washed off with water and a few drops of Gabbett's solution (methylene-blue, 2; sulphuric acid, 25; water, 75) are placed upon it and allowed to remain a minute or two. The specimen is again washed with water, and should then be uniformly blue; if not, a little more Gabbett's solution is added as before. In this method the carbolfuchsin stains everything, including the tubercle bacillus; the sulphuric acid of the second solution decolorizes everything but the tubercle bacillus; and the methylene-blue at once stains the cells and other elements, leaving the bacilli dark red. Even more satisfactory results may be obtained by allowing the carbolfuchsin to stain at ordinary temperatures for twelve hours; and in the staining of bacilli in tissues this prolonged cold staining is particularly desirable. Gram's method

gives positive results. Pappenheim's solution or repeated treatments with absolute alcohol are necessary when it is desired to exclude smegma bacilli.

Distribution of the Tubercle Bacillus.—This organism is probably a pure parasite, occurring and multiplying only in the body or excreta of diseased individuals, human or animal. Sputa or other excreta containing the bacillus may dry and retain the bacillus in a dormant though still potential form for long periods of time, outside the body. Multiplication of the organism, however, probably very rarely occurs, except within the body. The bacillus is found in the lesions of all parts of the body.

Modes of Infection.—The bacillus may gain access to the body either by direct inoculation, by the inhalation or swallowing of the germs, or by intra-uterine transference through the placenta. Direct inoculation through external wounds is perhaps more frequent than is believed. Definite lesions of the skin have been caused by vaccination, and are not infrequent upon the hands of anatomists in the form of the so-called anatomical tubercles. In some of the cases of scrofulous glands of the neck in children it is likely that the bacillus gains entrance through abrasions of the skin or of the mucous membrane of the mouth or pharynx. Genital tuberculosis is quite possibly frequently produced by direct implantation. The most common form of infection is through the inspired air. The breath of phthisical patients does not ordinarily contain bacilli, but the dust of rooms in which tuberculous patients have lived may contain numerous bacilli in a dry state, and these readily become mixed with the air and are thus inhaled. Tuberculosis of the lungs or, more rarely, of other parts of the respiratory tract is thus produced in susceptible persons. Despite the activity of some investigators to inculcate the intestinal tract in the origin of all lung lesions, it is now generally accepted that most pulmonary tuberculosis arises by inhalation. The bacilli lodge upon the mucosa, are taken into it, or by lymph-radicals, and carried to nearby lymph-nodes. Occasionally they reach the smaller bronchi and start the lesion there. The swallowing of tuberculous material may lead to tuberculosis of any part of the gastro-intestinal tract by the direct inoculation that results. Thus intestinal tuberculosis in particular is produced. Sometimes, however, the bacilli pass through the wall of the intestine and cause a primary lesion in the lymphatic glands of the abdomen, and it is not improbable that even the mesenteric lymphatic glands may escape without discoverable lesion or wholly, and the final lodgment of the infecting organism may be the lungs. The bacilli are swallowed with milk or meat, or they may gain access to the mouth, in the form of dust or particles of various kinds, and be swallowed with the saliva. Some assert that tuberculosis of the tonsil is of alimentary origin.

The milk and meat of infected cattle frequently contain bacilli, and undoubted instances of infection in this way have occurred. The proof of this is that in some cases of abdominal tuberculosis in young children the organisms obtained in cultures have shown the characteristics of the bovine species.

The intra-uterine transmission of tuberculosis is rare, but does occur. Most of the cases, however, of tuberculosis in early life may be explained as postnatal infections through milk, inspired air, etc. Some authorities assume that a few tubercle bacilli transferred from the mother to the fetus may lie dormant in the fetus and child and later cause active infection. This hypothesis rests upon no demonstrated facts.

Relation of Human to Animal Tuberculosis.—Tuberculosis attacks the lower animals with varying frequency. It is most common in cattle, and because of the peculiarities of the bacilli and lesions this form of the disease is termed "bovine tuberculosis." Many experiments have been made to establish the relation existing between the bovine and human forms of the disease, and Koch, in 1901, made the statement that the two were different diseases and probably were not intercommunicable. Ravenel disproved this assertion by producing the disease in cattle with bacilli obtained from human sources, although the animals exhibited a high grade of resistance to such an infection. At the same time he reported 4 cases of accidental local infection in man with the bovine bacillus. He, therefore, maintains "that human and bovine tuberculosis are but slightly different manifestations of one and the same disease, and that they are intercommunicable."

The present situation of the subject is best illustrated by the results of Park and Krumwiede. After exhaustive studies of the literature and their own material, these authors conclude that while bovine infection for the adult is practically negligible, in children a noteworthy percentage of tuberculosis of glands, abdominal organs, and meninges is due to the bovine tubercle bacillus. There is no positive proof now at hand to show a mutation from one type to the other.

Less frequently tuberculosis occurs in hogs, goats, horses, dogs, cats, sheep, rats, guinea-pigs, and rabbits. All these animals are more susceptible when kept in confinement. Captive monkeys are highly susceptible. In all these animals the disease is probably intercommunicable with human tuberculosis, but the lesions are not always identical with those found in the latter disease. Birds and fowl of various kinds are susceptible, though the disease is somewhat different in them from that seen in man. (See Fowl-tuberculosis.) Tuberculosis of cold-blooded animals has also been recognized. The form of disease in the latter is atypical, and the bacillus shows peculiar characteristics, but tends to approach the form of the human bacillus by successive passage through animals.

Animals may become infected from man, and may further spread the infection by their discharges and excretions. In the case of cattle the danger of dissemination is particularly great, because of the danger to man of infection through the digestive tract by means of tuberculous milk or meat insufficiently cooked.

According to the best testimony available at the present time it seems likely that the human, bovine, avian, and other animal species are simply variations of one common bacterial organism. Not im-

probably the peculiar characteristics may be acquired in the human body or the animal after the original infection. Thus the proof of the original source of the infection may be lost.

Pathological Anatomy.—Tuberculosis is characterized by the eruption of small nodules, varying in size from 1 to 2 mm. in diameter to that of a small pea. These are known as *miliary tubercles*. As already mentioned, the latter in gross appearance are not distinctive of tuberculosis, as similar nodules are met with in other diseases. Besides the tubercle there are *inflammatory lesions* occurring between the tubercles and varying with the anatomical character of the organs affected. Thus in the lungs the tubercle may be inconspicuous, whereas the pneumonic infiltration of the lung tissue surrounding the tubercles and filling in the spaces between them gives the organ its most striking anatomical characters. There are instances of tuberculosis in which the whole process runs its course without the development of any definite tubercles. For example, in the lungs the inhalation of tubercle bacilli in considerable numbers may be followed by rapid tuberculous pneumonia without definite tubercles, and in other situations similar results may be produced. In the further progress of a case of tuberculosis *caseous change* is important. This may present itself in the form of areas of considerable size having a dull, opaque, lusterless, grayish or whitish character, and not inaptly likened to the appearance of cheese. These centers of caseous necrosis may finally become liquefied, and cavity formations may result. These changes are particularly frequent in tuberculosis of the lungs, less frequent in bones, skin, glands, or kidneys. In connection with tuberculosis of bones there may be formed small or large cavities filled with liquefied caseous or puriform material. These may involve the surrounding tissues as well as the bones themselves. The term "cold abscess" is applied to them. Small tuberculous areas and sometimes even large foci are prone to be surrounded by reactive fibrous-tissue hyperplasia, and thus a complete encapsulation may result. Small foci may be uniformly transformed by organization of proliferating connective tissue and may be thus entirely healed. In other cases simple encapsulation occurs, the tuberculous mass within perhaps undergoing calcification. These changes will be more particularly referred to below.

Tuberculous lesions of the mucous membranes frequently begin with the formation of distinct tubercles occupying the deeper layers of the mucosa or the submucosa. These by confluence may form considerable areas of tuberculous disease, while at the same time reactive inflammation of the surrounding tissues adds to the mass. Sooner or later ulcerative changes upon the surface make their appearance, and irregular, more or less necrotic, ulcers result. The caseous appearance of these and the occurrence of distinct tubercles in the edges or base manifest the character of the process.

The histogenesis and anatomy of the tubercle has been considered on page 141, and we shall only here consider its pathological relations.

After the establishment of the local lesion of tuberculosis in any

part of the body two opposing tendencies struggle for supremacy: the tendency of the tuberculous disease to spread and the tendency of the normal tissues to encapsulate or limit the spread of the invading disease. In most cases the former succeeds and the secondary tubercles first appear in adjacent parts, the transportation of the bacilli from the primary to the secondary focus being accomplished either by the flow of the lymph or juices of the body, by continuity, or by the activity of phagocytes. The last take from the edges of the tubercle some of the bacilli and transport them either by their own ameboid activities or in the lymph-stream to neighboring parts, where they themselves fall victims to the organisms they have appropriated, and thus deposit the germs of new foci of disease. The dissemination of tubercles to more distant parts may occur in various ways. In the case of tuberculosis of the mucous membranes bacilli may be cast off from the surface and spread to other parts of the mucous tracts with the contents of these, as in the case of tuberculosis of the gastro-intestinal tract. In the case of pulmonary lesions the ulcerative processes, or attacks of coughing, may loosen infected particles from lesions of the bronchi, and the deep inspiratory efforts following the cough, or the ordinary inspirations, may carry the bacilli into the finer bronchioles, where new foci arise. If the tuberculous lesions involve the walls of the lymphatics, particularly the larger lymph-channels, like the cervical or thoracic ducts, bacilli may gain access to the lymph-stream and thus be transported to the venous circulation, and then through the heart to the lungs or perhaps to other organs. When the tuberculous lesion invades the wall of a vein the dissemination of the bacilli is even more rapid and widespread, as the organisms find their way to the heart by a more direct route. In rare instances an artery is invaded and the organisms are scattered through the terminal distribution of this. The lesions of vessel walls arise either as primary tubercles, as extension processes, or secondary to intimal lesions leading to thrombosis, a condition which favors the settling of tubercle bacilli. Upon surfaces the disease may spread by direct continuity or by the movements of the body. Thus, lesions of the peritoneum may become almost universal in consequence of the peristaltic movements, though more frequently the extension occurs along the lymphatic channels.

The condition which results from general infection and formation of tubercles in various situations is known as *miliary tuberculosis*. In these cases the progress is usually rapid and a fatal termination is not long delayed. The tubercles, therefore, remain small, and at autopsy are still typically gray miliary tubercles. Sometimes, however, miliary tuberculosis may assume a more chronic form, perhaps in consequence of the gradual admission of bacilli to the circulation and the formation of small crops of tubercles during a considerable period of time.

Occasionally, tubercle bacilli invade the blood and do not give rise to miliary tuberculosis. Why they do not is not clear.

Miliary tuberculosis may be local or general. In the former case the bacilli are admitted to the vascular distribution of a restricted

area only; in the latter, widespread dissemination through the blood occurs, and practically all parts of the body may be involved. Localized miliary tuberculosis is most frequent in the lungs.

The progression of tuberculosis is accomplished by the coalescing of formed tubercles or an exaggeration of the inflammatory characters, especially in the presence of mixed infection, or to both. Regressive tuberculosis is either latent (*q. v.*) or cicatrizing. The latter is that form in which the most pronounced lesion is fibrous tissue formation, which may or may not finally wholly replace the tuberculous tissue. Such a process is responsible for the healing of tuberculosis. It has been asserted that two-thirds of all adults have some such healed lesion of tuberculosis in them.

The healing of tuberculous lesions follows the general rules of repair. The fibroblasts grow both within and without the tubercle and gradually replace it. Wherever fibrin has been deposited the tubercle grows and attempts to form a new tubercle. It is noteworthy that in healing of tuberculosis a great amount of fibrous tissue is produced and adhesions are common.

Seats of Tuberculosis.—Among the frequent situations in which tuberculosis makes its appearance are the lungs, the lymphatic glands, the bones and joints, the mucous membranes, particularly those of the larynx and intestines, the serous membranes, the prostate, testicles, ovaries, Fallopian tubes, kidneys, uterus, suprarenal capsules, brain, liver, spleen. In some of these situations the lesions are practically always secondary, as, for example, in the liver and spleen. In others they are most frequently primary, as in the lungs. The occurrence of primary tuberculosis in the internal organs may be difficult to explain. It is possible, however, for the bacilli to gain access to the lymphatic or blood circulation without causing a lesion at the point of entrance. Their deposit in some internal organ then occasions the first or primary focus of disease. Thus, primary tuberculosis of the mesenteric glands, of the lymphatic glands of the neck, or of the postbronchial glands may occur without primary disease of the intestines, of the mouth or skin, or of the lungs in the several instances. Similarly, primary tuberculosis of the kidney or of the suprarenal capsule may occur without any evidence of the point of entrance of the micro-organisms. In some cases, of course, the primary lesion may be so small and in such a hidden situation that it escapes notice.

After the discovery of the tubercle bacillus a number of diseases not previously recognized as tuberculous became identified as forms of this disease. Among these is *lupus vulgaris* of the skin. The histological examination shows numerous tuberculous granulations, sometimes arranged in striate fashion along the small blood-vessels of the skin and containing epithelioid and lymphoid cells and giant cells. The presence of the bacilli and the proved infectiousness of the tissue, with the histology, render the nature of this disease certain. The warty formations frequently acquired by anatomists at points of injury have likewise been shown to be in many cases due to tuberculous infection.

Scrofula, which was formerly regarded as a special condition predisposing strongly to tuberculosis, is now regarded as actual tuberculosis. The scrofulous glands of the neck constitute tuberculous adenitis, the infection in many cases gaining access through the mucous membranes of the mouth and pharynx or through the skin. Scrofulous rhinitis and sinuses have similarly been shown to be forms of tuberculous disease. Many cases of joint disease regarded as scrofulous are likewise dependent upon the action of the tubercle bacillus.

Latent Tuberculosis.—A tuberculous lesion may become encapsulated and limited in its extent before it has invaded tissues widely, and may so remain for years without giving rise to manifest clinical symptoms. Subsequently, however, the encapsulating membrane may be penetrated and widespread infection, local or general, may occur. Such latent tuberculosis is particularly frequent in the postbronchial glands. These glands are often found enlarged at autopsies in which no tuberculous disease of other organs is found. Injections of emulsions of such glands in a notable proportion of cases produce tuberculosis in guinea-pigs, and thus it has been determined that the glands in question are frequently the seat of latent tuberculous disease. The existence of such lesions explains the cases of sudden generalized miliary tuberculosis, in which no primary focus of the disease was recognized during life. It is perhaps well to emphasize the difference between latent and healed tuberculous foci. The former are arrested and surrounded by a limiting wall of connective tissue through which it is possible for degenerations or inflammations to extend and free the tubercle bacillus, or awaken it to activity, while in healed foci it is assumed that all infective agents have been destroyed, and the original lesion wholly replaced by fibrous tissue.

Pathological Physiology.—The effect of tuberculosis upon the general health varies greatly. Undoubtedly the bacillus contains or is capable of producing toxic substances that have an effect upon the general organism; the nature of these, however, still remains undetermined. The tuberculin of Koch, a glycerin extract from cultures of the tubercle bacillus, produces fever with the general symptoms characteristic of pyrexia and local reactive changes in existing tuberculous lesions. Among the latter, redness or increased vascularization of the tubercles, and softening or necrosis of the cells surrounding the bacilli, are most important. The last named change deters the growth and multiplication of the bacilli themselves, but at the same time makes their escape from the focus of disease more easy and thus exposes the individual to the liability of general infection. The active substance contained in tuberculin is probably a thermostabile polypeptid that is destroyed by pepsin and trypsin, but not by erepsin. It is positively chemotactic for leukocytes. It does not act upon the tubercle bacillus directly and is not an anti-toxin. The tubercle bacillus seems able also to excrete lipase during its vegetative life. In addition to this, the tubercle bacillus in its dead state contains some body or bodies capable of influencing the organism, as was shown by the experiments of Prudden and Hodenpyl, who

were able to produce nodular lesions by injecting dead bacilli into the circulation of animals. Mention has already been made under Caseation of the unsaturated fatty acids of tubercle bacilli in the production of necrosis. Such substances are also present in dead bacillary bodies. These lesions, of course, are not strictly tuberculous, though they possess some elements of the natural tubercle. It is altogether probable, however, that in addition to the tuberculin of Koch and the chemotactic substances contained in the body of the tubercle bacilli, there are other poisonous substances produced by the growth and multiplication of the bacilli in the tissues, that lead to a general deterioration in the health of victims of this disease. Trudeau, Pearson and Gilliland, and others have been able to immunize animals by repeated inoculations with bacilli of lowered virulence. Human bacilli if injected into cows will raise their resistance to virulent bovine bacilli. A form of immunity called "isopathic" (Behring) is thus produced. The sera of such immunized animals is not protective or curative to other animals.

None of the supposed "antitoxic" sera thus far produced has been proved to have antitoxic or immunizing power.

Tuberculosis is primarily a local process, but influences the general organism by its direct effect upon the organic functions of the parts in which it is located by the development of these as yet unknown toxic substances, and later by the widespread infection of the organism. Amyloid disease is a sequel of prolonged tuberculosis. The mechanism of defence against tuberculosis is only partly known. In the case of local lesions of the lungs or other parts the reaction of the tissues probably resulting from the activity of chemotactic substances in the body of the bacilli themselves, or of similar substances produced by the cellular necrosis, leads to the formation of an embankment of cellular or fibrous tissue that serves to hold the disease in check. Subsequently, the disease may be wholly eradicated by degenerative changes terminating in calcification. That such favorable results are not uncommon is proved by the frequent occurrence at autopsies of small sclerotic or calcareous areas in the lungs. Tuberculosis is frequently cured in these early stages, but after it has reached the degree of intensity or the widespread character that makes it recognizable by our present methods of physical examination, the reactive processes are usually no longer able to cope with its progress.

The defensive reactions of the blood against the tubercle bacillus are not very potent. In the serum there appear agglutinins, opsonins, and a complement-fixing body in excess of those found in non-infected persons. Use is made of the opsonins in bacterin therapy, as it is possible to increase their strength by injection of some of the products of the tubercle bacillus or of killed cultures. Repeated injections of the bacilli or their products into lower animals have not developed any valuable antisera for therapeutic purposes, but claims have been made that active immunization with living bacilli will raise the resistance of animals and man. Such methods are, to say the least, hazardous.

PSEUDOTUBERCULOSIS

This name has been applied to conditions occasionally met with in which nodular lesions resembling tubercles, but containing micro-organisms of different kinds, have been found in the liver, kidneys, and other organs. Pseudotuberculosis is not a specific disease, as a number of distinct infections assume this pathological character. Among the organisms isolated are various streptothrices and acid-proof bacilli resembling the tubercle bacillus to some extent (see below). In the lower animals, and very rarely in man, certain animal parasites cause lesions of the same kind.

The Smegma Bacillus.—A bacillus quite closely resembling the tubercle bacillus was discovered in the smegma and later on the skin of various parts of the body. It not only resembles the tubercle bacillus morphologically, but behaves in a similar manner toward stains. In particular this bacillus holds its stain when attempts are made to decolorize with acids. The bacillus is frequently found in urine, and thus may cause an erroneous diagnosis of tuberculosis of the kidney or bladder. It may usually, though not certainly, be distinguished by its easy discolorization with absolute alcohol.

Other Acid-proof Bacilli.—Several other bacilli that are refractory to decolorization with acid or alcohol have been discovered in milk and butter, in sputa, and in purulent or gangrenous collections in the lungs and elsewhere. Injections of pure cultures of some of these cause fibrinous inflammations in the peritoneum of guinea-pigs and rabbits, or pseudotuberculous formations, but not the specific lesions of tuberculosis.

The lesions resulting from inoculation with acid-fast bacilli show a striking resemblance to those of tuberculosis, and only a careful microscopical examination serves to distinguish them. Examined with a microscope, the lesions of this spurious tuberculosis present a more inflammatory appearance and show a tendency toward abscess formation. In very rare instances, however, an approach toward the typical histologic conditions of genuine tuberculosis, characterized by the formation of giant cells, epithelioid cells, and caseation, is seen in this form of pseudotuberculosis.

The causative organisms in such infections range in a biological series from short, bacillary, rigidly acid-fast forms very like tubercle bacilli to longer threads slightly acid fast, to groups of higher bacteria growing in mycelia and not acid fast, related to actinomyces and streptothrix.

The streptothrices may produce infiltrative and proliferative lesions like the organisms just discussed. They have been found in various parts of the body as the causative factors in abscesses. The lung process is infiltrative, then suppurative, then necrotizing. Some of the streptothrix infections may resemble pulmonary tuberculosis and can be diagnosed only by isolating the organisms or by skin tests. It has been found possible to differentiate the various infections with these higher bacteria by means of skin tests. Preparations made from cultures of the various organisms, tubercle bacilli, partly acid-fast organisms, and those of streptothrix type, are rubbed upon an abraded skin surface; a swollen red area will arise in response to the preparation made from the causative bacterium and not to others.

Pneumomycosis aspergillina.—In man and in animals pulmonary infection with forms of aspergillus, especially *Aspergillus fumigatus*, may occur in a pseudotuberculous form. The lesions are exudative and proliferative, and central caseation may be conspicuous. The fungi which belong to the group of *hyphomycetes* are readily distinguished by the abundant mycelial threads and the conidia. Infection of other organs may occur spontaneously or experimentally.

Pharyngomycosis leptothricia.—The *Leptothrix buccalis* is a normal inhabitant of the mouth, and occasionally produces a pathological lesion

of clinical interest. The organism probably belongs to the group of pleomorphic bacteria, though its exact position is not determined. It consists of fine threads, of wavy or spiral character, composed of rod-like segments. Occasionally spore-like bodies are found at the free ends of the filaments. The organism sometimes penetrates and multiplies in the crypts of the pharynx, causing a chalk-like nodule or deposit. Secondary inflammation may be occasioned. (See also Diseases of the Pharynx.)

FOWL-TUBERCULOSIS

Tuberculosis in various forms of fowl and birds (avian tuberculosis, Tuberculosis gallinarum) is a disease similar to, but not identical with, human tuberculosis. The spontaneous disease of birds occurs most frequently in the liver, the lungs being never primarily involved. In the liver are found nodules composed of a large central necrotic area sprinkled with chromatin debris surrounded by a zone of large epithelioid cells containing numerous nuclei, intermixed with small round cells. Tubercle bacilli are present in enormous numbers. The structural and cultural differences of the human and avian bacilli have been discussed on page 315.

Despite the similarity of the bacilli of the human and avian types of tubercle bacilli, it does not seem that the latter can produce tuberculosis in man. In the few cases in which avian bacilli have been isolated from human lesions, the simultaneous presence of human bacilli was not satisfactorily excluded.

Experimental inoculations of bacilli isolated from the spontaneous disease will produce the same disease in birds; but if animals, such as guinea-pigs or dogs, which are very susceptible to human tuberculosis, are inoculated, they frequently resist infection, though they occasionally succumb to very large doses. In the latter case tubercles are usually absent, but large numbers of bacilli are found in the organs and in the abscesses which result at the point of inoculation. According to Nocard, rabbits show a marked degree of susceptibility to this form of tuberculosis.

Although there is no doubt that fowl in some instances have become infected through human sources, yet experimentally they exhibit a very high degree of resistance to human bacilli. If, however, the human bacilli are passed through birds for three or four generations, or are placed in the peritoneum of fowl in collodion sacs, for the same length of time, the virulence to birds is not only heightened, but the bacillus changes in its structural and cultural characteristics, assuming those of the bacillus isolated from spontaneous avian tuberculosis. The same is true of avian bacilli when these are inoculated in animals susceptible to human bacilli. With each passage through such an animal the virulence of the bacillus is increased, and the form and cultural characteristics become more and more like those of the human bacillus. From these experiments it appears that the avian tubercle bacillus is only a modification of the ordinary tubercle bacillus caused by its growth in the tissues of the bird.

LEPROSY

Definition.—Leprosy, lepra, or elephantiasis Græcorum, is an infectious and mildly contagious disease caused by a specific bacillus, the *Mycobacterium lepræ*, discovered by Hansen.

Etiology.—The essential cause of leprosy is a bacillus which closely resembles the tubercle bacillus, though it is less frequently curved and is somewhat more easily stained. Further, it differs in its grouping in the tissues and in its character of growth. The organism is usually found in large numbers in the leprosy lesions and in the nasal mucus, whether there be definite leprosy ulcerations in the nose or not. In the tissues the bacilli are found within large cells of the specific granulation tissue (lepra cells). In the anesthetic form it is found in the nerves and central nervous tissues. The organism has been demonstrated in the blood in certain cases of the tubercular type. It is readily stained by any of the methods applicable for the tubercle bacilli or by Gram's method. It frequently shows light areas like those of the tubercle bacillus; these have been regarded as spores, but are more probably produced by fragmentations, as in the case of the tubercle bacillus.

Musgrove, Clegg, and Duval have succeeded in cultivating the leprosy bacillus upon media containing tryptophan. The organisms do not possess the power of digesting the protein molecule to liberate this substance, so that it must be introduced artificially or supplied to them by means of symbiotically growing amebæ or bacteria. Two kinds of cultures have been observed, one growing in a luxuriant yellow form, the other as a scanty, almost colorless colony. The importance of the two is not yet understood. Some believe that the scanty growth is the true lepra bacillus. Wolbach and Honeij's work upon human and rat leprosy would suggest that four kinds of organisms—diphtheroids, pigmented acid-fast, non-pigmented acid-fast, and anaerobics—have been cultivated in different parts of the world. It would seem that they may all be involved, or that two are present as varying examples of one organism. What has been called typical leprosy has been produced in rabbits' eyes, mice, and especially monkeys. Flies of the genera *Musca* and *Stomoxys* have been accused of carrying lepra bacilli. In one case the disease has been given to a condemned criminal by direct inoculation.

Besides the specific bacillus, other conditions are important in the etiology. Thus, the disease flourishes in certain localities extensively and little in other places. It is uncommon in the United States, but some of the Gulf States, particularly Louisiana, have considerable colonies, and in the Northwest and on the Pacific Coast it is met with among the Norwegian and Chinese immigrants. In Mexico, South America, Norway and Sweden, India, and other Asiatic countries it is common, and the Sandwich Islands are particularly affected. During the Middle Ages it flourished in Europe as a universal scourge, unsanitary conditions probably acting as the predisposing cause. Certain articles of diet are believed to occasion it, particularly fish; this view, however, lacks proof.

The disease must be regarded as contagious, though less so than tuberculosis. Intimate association for a long time seems to be necessary for its transference. Insects have been thought to transmit the disease, but proof is as yet not forthcoming. It is probably transmitted from parent to offspring in rare instances. The bacilli have been found in the hyalin substance, the syncytial cells, chorionic villi, and vessel walls of the placenta.

The importance of the nose as a seat from which leprosy bacilli are disseminated is emphasized by the facts that the bacilli are present



Fig. 115.—Nodular leprosy (Goldschmidt).

here even when no leprous lesions exist, and that ulcers are common on the septum. The lesions when present are softer than those on the skin and may be found in both the tubercular and anesthetic forms.

Pathological Anatomy.—Leprosy presents itself in two forms—the *tubercular* and the *anesthetic*. In the former there are developed in the skin of the face, the extensor surfaces of the elbows and knees, about the hands, or less frequently elsewhere, small or large nodular elevations. These at first are reddish in color, with apparent inflammatory reaction. Later they lose their redness and remain as indolent lesions that grow very slowly or remain stationary. They may break

down, forming ulcerations which do not readily heal, or they may be gradually converted into fibrous cicatricial tissue, causing unsightly deformities of the skin. The appearance of the patient's face is highly characteristic, and is known as *leontiasis leprosa* (Fig. 115). The mucous membranes and some of the internal organs may be involved. The anesthetic form is usually marked by less conspicuous lesions, but subjective symptoms, such as hyperesthesia and neuralgic pains, and later ulcerations partly trophic in nature, may make it a more serious variety. In the skin there are found whitish or brownish spots, slightly if at all elevated or altered in consistency. Later, ulcerations may appear. Very commonly the anesthetic and tubercular varieties are coexistent.

The chief seats of the leprous nodule are in the corium and sub-mucous tissues. It invades, by cellular extension, the adjacent nerves, vessels, muscles, and sweat-glands, and may be found in the epithelial coverings.

The nodules occurring in the liver, spleen, and testes in this disease are admitted to be similar to the nodules of the skin; those found in the lungs, kidneys, and intestines, as well as those of the serous surfaces, are believed by many to be tuberculous and the result of secondary infection. These two diseases are certainly frequently associated; probably 40 per cent. of the cases of lepra become tuberculous.

Other forms of secondary infection occur. Thus injuries of superficial lesions may allow pyogenic infection, and extensive ulcerations and gangrenous necrosis may ensue. The terms *lepra mutilans* and *lepra gangrænosa* are applied to such; and various micrococci and saprophytic organisms have been discovered in such cases. The histology of leprosy is given on p. 147.

Pathological Physiology.—Infection with the lepra bacillus leads to local rather than general disturbances. The toxins of the disease, if such there be, are not of great virulence, and constitutional symptoms are, therefore, wanting as a rule. In the later stages fever and other systemic disorders may be occasioned by secondary infections. A supposed antitoxic substance has been prepared and has been largely used. It is impossible to claim or disclaim the antitoxic nature of this, as no toxins have as yet been isolated or obtained in any form, and the supposed antitoxic substances cannot, therefore, be tested.

In the anesthetic form it was formerly customary to regard the pigmented or light-colored spots as a result of trophic disturbance, and more destructive lesions, such as ulceration and gangrene, received a similar explanation. Recent investigations, however, seem to show that in these cases there is usually from the first a leprous change in the tissues due probably to thickening of vessel walls, and that secondary infections frequently play a part, though trophic disturbances must still be admitted to a certain extent.

BACTERIUM MUCOSUM CAPSULATUM GROUP

This is a very large group, chiefly saprophytic, in the intestinal tract of men and animals, but includes a few important highly pathogenic varieties. They are all Gram-negative, non-motile, blunt-end rods, growing luxuriantly on artificial media, and with active ferments against carbohydrates. Some possess capsules in the body only, others in certain artificial media as well. Perkins divides them into three convenient groups:

(a) The *Bacterium aërogenes* type ferments all carbohydrates, with the formation of gas.

(b) *Bacterium pneumoniae* type ferments all except lactose, with gas.

(c) *Bacterium lactis aërogenes* ferments all as above, except saccharose.

This order represents their frequency and pathogenicity. The first class is found in abscess, pneumonias, and inflammations of serous membranes. The most important member of the second group is commonly called "Friedländer's bacillus," an organism seldom found aside from pneumonia. (See Friedländer's Pneumonia, p. 283.) The third group contains very few pathogenic varieties, but is most commonly concerned in milk souring.

The exudates caused by all the pathogenic members of this group have one or both of two characters. The exudate may be viscid or it may contain swelled up cells in which the organisms lie (Mikulicz cells and swollen cells of Friedländer's pneumonia). The bacteria possess a mild lytic effect upon epithelium and endothelium. The organisms give rise to very few antibodies.

A very important non-pathogenic organism not far removed from the third division is the *Bacterium bulgaricum* of Massol. This breaks up the carbohydrates of milk and produces lactic acid. This is recommended by Metschnikoff as an intestinal antibacterial agent.

Other Organisms of Less Importance

The *Bacillus pyocyaneus* is a Gram-negative, occasionally pathogenic organism found in pus having a bluish or greenish color. The bacillus is small in size, frequently occurring in chain formation, and is actively motile.

Upon artificial media it produces colored growths and a soluble pigment, which gives to the culture-medium for some distance from the growth a greenish, or in some cases a dark blue, coloration. The organism in pure culture is highly virulent, producing intense suppurative inflammations. Occasional instances of general pyocyaneus infection have been observed. In these cases there are most commonly thin purulent exudates in serous cavities and cellulitis.

The organism acts destructively upon other bacteria, so that a fatal dose of *Bacillus anthracis* may be rendered innocuous by the simultaneous injection of *B. pyocyaneus*. The destructive effect has been demonstrated *in vitro*. It seems dependent on ferments as well as intracellular substances contained in the bacillus. The toxin is hemolytic and parenchymatous degeneration arises in the liver, kidneys, etc.

DISEASES DUE TO SPIRILLA

CHOLERA

Definition.—Cholera is an acute infectious disease caused by a spirillum or vibrio.

Etiology.—The specific cause of cholera is the *Spirillum* or *Vibrio cholerae asiaticæ*. This organism is frequently spoken of as the comma bacillus of Koch. It is a short rod, from 0.8 to 2 μ in length, and usually somewhat curved. The term “comma bacillus” is applied to it on account of the latter fact. It is found abundantly in the rice-water discharges of choleraic patients, and is not rarely arranged in threads, though the vibriones are not actually attached to one another (Fig. 116). It is motile, the motility being due to a single flagellum attached at one end. In artificial cultures the organisms are actually joined to form



Fig. 116.—*Spirillum* of Asiatic cholera, from a bouillon-culture three weeks old, showing numbers of long spirals; $\times 1000$ (Fränkel and Pfeiffer).

spirals of greater or less length, and these may present a rapid rotary movement.

The demonstration of the cholera spirillum is usually easy, as ordinary stains color it intensely. It is Gram-negative. Even the flagellum may be stained by the ordinary stains, though more definitely shown by special methods.

The cultivation of the spirillum is usually easy. Cultures may be obtained upon agar-agar, blood-serum, or other media, but the gelatin-culture is most characteristic. In puncture-cultures the growth occurs along the entire length of the puncture, but particularly at the top, where the supply of oxygen is abundant; and the gelatin becomes liquefied. This gives rise to a peculiar nail-shaped or funnel-shaped formation (Fig. 117). In plate-cultures the growths first appear in the lower

strata of the gelatin as small granular whitish spots which extend toward the surface, liquefy the gelatin, and thus produce excavations. The appearance to the naked eye suggests small air-bubbles in the media. Under low powers of the microscope the culture is seen to be coarsely granular, the size of the granules varying with the age of the culture. The bottom of the growth presents an appearance like that of a surface sprinkled with powdered glass.

When grown in bouillon or other liquid media the cholera microbe produces nitrites and indol so abundantly that the addition of a little pure sulphuric acid or hydrochloric acid (without nitrite solution) leads to a reddish coloration—"cholera-red." The indol reaction is not absolutely diagnostic, since other spirilla may cause it. Negatively, however, the test is extremely useful, since its absence excludes the cholera germ. A definite quantity of peptone is necessary to make the test reliable. Therefore, instead of bouillon an alkaline 1 per cent. peptone solution containing 0.5 per cent. of sodium chlorid is preferable (Dunham).

The cultures of cholera grow best at a temperature about that of the body, but they may thrive at much lower degrees of heat. Exposure to a temperature of 52° C. (125.6 °F.) for four minutes may cause their destruction, but ten or fifteen minutes' exposure at 55° C. (131° F.) does not always prove destructive. They may thrive in distilled water or in water containing saline matter; in or upon various forms of food; upon clothing, and the like. The resistance, however, is not very great, and this has been urged as an objection to the likelihood of the organism being the cause of a disease having such evident tenacity.

Distribution.—The cholera spirillum is found in the intestinal contents and mucosa. The organism is not found in the blood nor in any organ or tissue except the gastro-intestinal tract.

The **pathogenicity** of the cholera spirillum is now admitted universally. Injected into the peritoneum of animals it causes a rapid fall of temperature, abdominal tenderness, and collapse. The peritoneum shows signs of beginning inflammation, and the organisms are found in abundance within the cavity. It has been possible also to produce intestinal changes almost if not identical with those of human cholera in animals by arresting the peristalsis of the intestines with injections of opium, rendering the liquids of the stomach alkaline with sodium carbonate, and then feeding cultures. In man a few auto-infections have occurred, the experimenter swallowing cholera cultures. In one case at least typical cholera was admitted by Pettenkofer, the most important opponent of the acceptance of this germ, as the specific cause. The celebrated case of Dr. Oergel, who died as a result of laboratory auto-inoculation, seems practically conclusive.

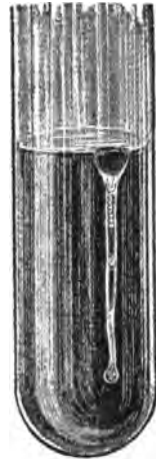


Fig. 117.—Puncture-culture in gelatin of spirillum of cholera; sixty hours old (Shakespeare).

Other Causes Operating in Cholera.—Infected water is the chief source of transmission of cholera. The microbe may live in water for months. It is said that the Ganges River contains the spirilla constantly. Certain climatic conditions favor the development of the disease. Thus it is constant in certain regions of India, and spreads thence when the conditions become favorable. The evidence shows that the germ is carried by individuals, or by infected food and the like. The disease flourishes in warm seasons of the year, and an epidemic is usually brought to a close by winter frosts.

Individual disposition plays a part in the occurrence of the disease, for the germ is easily destroyed by the acid gastric secretions, and infection is, therefore, most likely to occur when gastro-intestinal derangements furnish a favorable predisposition.

Pathological Anatomy.—The lesions of this disease are found in the intestinal tract, and will be described in the appropriate section.

Secondary lesions of other organs are met with in severe cases, and result from the circulation of toxic substances produced by the bacillus.

Pathological Physiology.—A number of toxins have been isolated from the blood of cholera patients and from cultures. The exact nature of these and the relations of the several forms remain to be determined. It is certain, however, that toxins produced in the intestinal tract give rise to many of the symptoms of the disease. Injection of the filtrate of cultures causes collapse and other symptoms like those of the algid stage of the disease. The principal toxic substance seems to be closely attached to the organism itself (endotoxin), but a secreted extracellular toxin may also be found in the culture fluid when the organisms are enclosed in a collodion sac. The human or animal organism in some way develops immunizing or protective substances in the course of infection, and it has been found possible by a process of vaccination with cultures of gradually increasing virulence to protect animals and human beings from the disease. Haffkine's protective vaccination of human beings yielded very encouraging results. He at first used an attenuated culture and then one of high virulence. The injections are made under the skin, where the spirilla soon die, but their bodies set up the antibodies. He inoculated 200,000 persons in India. Pfeiffer found that the serum of animals so vaccinated had a distinct action upon cholera spirilla, causing their agglutination or destruction, and possibly in this way exercising a protective influence. These antibodies may be used to diagnose a case of cholera, either by agglutination, like the typhoid Widal test, or by the Pfeiffer intraperitoneal test.

The rapid and copious intestinal discharges of cholera lead to considerable inspissation of the blood, and doubtless contribute to the causation of some of the symptoms of the disease. Examination of the blood during the height of the malady may show greatly increased numbers of the red blood-corpuscles.

Organisms Resembling the Cholera Vibrio

Spirillum of Finkler and Prior.—This organism was discovered by the investigators, whose names it bears, in the stools of a case of cholera nostras. It resembles the vibrio of Asiatic cholera in its shape and somewhat in its manner of growth and its production of the indol reaction. It differs, however, in being somewhat longer and more slender and in coagulating milk when this is used as the culture-medium. The growth upon gelatin is more rapid, so that within twenty-four hours in the case of a puncture-culture the liquefaction has proceeded so far along the puncture that an elongated sac-like excavation is formed, in which turbid liquid is contained. It has not yet been proved that this organism has an etiological relation to cholera nostras; its pathogenicity is improbable.

Spirillum tyrogenicum is an organism discovered in old cheese by Denecke. It resembles the last-named variety very closely, and differs from the vibrio of cholera in liquefying gelatin quickly, though the rapidity is not so great as in the case of the Finkler and Prior organism.

Spirillum Metschnikovii.—This organism was discovered by Gamaleia in the intestines of chickens affected with choleriform disease. It is somewhat shorter and thicker than the cholera spirillum. In culture it resembles the vibrio of cholera very closely, though the trained bacteriologist can easily distinguish them. The organism is non-pathogenic for man, but chickens, pigeons, and guinea-pigs are highly susceptible.

Besides these spirilla or vibriones which have been discovered in various diseases, a number of organisms that resemble closely the spirillum of cholera have been found in the water of streams supplying the drinking-water of cities. Among these Neisser described the *Spirillum berolinense*, obtained from the water of the Spree in 1893. Dunbar and Oergel isolated a similar organism from the water of the Elbe, and a number of others of like character are known. The relations, however, of the different forms to each other and the differentiation of these varieties have not as yet been definitely determined.

Pathogenicity.—Some of the forms described produce violent gastro-intestinal disturbance and death in a certain proportion of animals prepared by injection of opium and alkalization of the intestinal tract with soda and then fed with pure cultures of the organisms. They are evidently highly irritating bacteria, and some remote relationship seems to exist between them. This, however, cannot be positively asserted.

The separation of these forms from the true cholera spirillum is by no means easy. It is best done by the agglutination and bacteriolytic tests. For this purpose it is necessary to have the serum of an animal immunized against the cholera germ, and to this only the cholera spirillum will react.

DISEASES DUE TO SPIROCHETES

SYPHILIS

Definition.—Syphilis is a specific contagious disease of man, believed to be caused by the *Spirochæta pallida* or *Treponema pallidum*. The disease does not occur spontaneously in any of the lower animals.

Etiology.—Many organisms have been described for this disease, the most discussed being Lustgarten's bacillus and Schaudinn's spirochete. The former is a large rod, said to lie in and between the cells of lesions, of general tubercle-bacillus-like morphology. It has not been cultivated. It has now been given up as the cause of syphilis.

In 1905 Schaudinn discovered an organism in syphilitic lesions which he named *Spirochæta pallida*. Later during the same year and with the co-operation of Hoffman he was able to demonstrate the organism in every case of uncomplicated syphilitic disease examined by him. The spirochete is described by Schaudinn (Fig. 118) as an extremely



Fig. 118.—*Spirochæta pallida* from chancre, stained by Levaditi's method; $\times 1500$ (Bulletin No. 1, Medical Department, U. S. Army, 1913).

delicate, actively motile, faintly refractive, spiral, long, thread-like organism, tapering at both extremities and terminating in pointed ends. It propels itself during life by rotating around its longitudinal axis, first in one direction and then in another. In the resting state undulating movements may be observed passing along the length of the organism, suggestive of an undulating membrane. In addition, bending, twisting, twining, and whipping movements of the whole body may be noticed. The organism varies from 4 to 14 μ in length, ranging in thickness from a size too minute for measurement to 0.25 μ in the largest specimens. The spirals range from six to fourteen in number; they are regular, narrow and deep, corkscrew-like, and appear constantly so, no matter whether the specimen be derived from initial lesions, papules, lymphatic glands, spleen, etc., or from the scleroses of apes. The curves are large

arcs of a small circle, while other spirochetes occurring with the pallida show smaller arcs of a large circle. By means of Löffler's method of staining flagella a long delicate flagellum has been noted at each end of the organism; in some specimens two flagella at one end were seen, giving the appearance of an attempt at longitudinal division. Novy could find no evidence whatever of longitudinal division. Schaudinn has failed to discover any signs of an undulating membrane or a nucleus in the stained specimens, though the latter has been reported by Weichselmann and Loewenthal in specimens examined with the aid of the ultramicroscope. At present there is some difficulty in distinguishing positively between the *Spirochæta pallida* and some common non-pathogenic forms. Too much weight cannot, therefore, be given to the discovery of spiral organisms unless the investigator has had considerable experience.

The *Spirochæta pallida* has been found in the initial lesions, the secondary papules, the enlarged lymphatic glands, the mucous patches, the secretions, blood, and lately, by Noguchi, in the parasyphilitic disease paresis.

Many of the most conservative authorities accept this as the cause of syphilis. As will be seen below practically all of Koch's postulates have been fulfilled.

Schaudinn maintained that the spirochetes are animal organisms belonging to the group of flagellates and proposed the name *Treponema pallidum*. The researches of Novy seem to be conclusive that this is not the case. He could find no evidence of an undulating membrane, nucleus, or longitudinal division, and, on the contrary, only the transverse fission characteristic of bacteria.

Wherever later studies place this spiral organism, certain characters have been made known by recent work suggesting its bacterial nature. It has now been cultivated by many persons after a technic elaborated by Noguchi. It grows anaërobically in colonies resembling those of bacteria and indicates its essential parasitic nature by requiring in this anaërobic culture fresh animal tissue. It does not require any intermediate stage to be infective, for, as we shall see, infection usually arises by direct contact, and, as the work of Noguchi has also shown, it will cause syphilitic lesions in rabbits' testes by inoculation of cultures, or of fresh material from human lesions. Syphilis can be produced in the anthropoid apes by inoculation of fresh human material or cultures upon the skin, and a skin affection will result from the same treatment in the lower monkeys. When animals are infected with syphilis by experimental methods, the spirochete can be recultivated from their lesions. The cultures at hand develop a protein-like body which has some relation to the infection, because when a sterile solution thereof is applied to an abraded skin area an inflammatory papule results. This is the so-called "luetin reaction," and it has been used as a diagnostic test. The results of this and the Wassermann or complement-fixation test (*q. v.*) indicate the active antibody formation on the part of the body. Agglutinins are also formed. All of

these recently discovered features favor a classification among the spirochetes.

Whatever the nature of the organism, it is quite certain that the disease is definitely infective. In the great majority of cases infection occurs by direct inoculation in sexual intercourse. It may, however, be conveyed in many other ways. Physicians are sometimes infected in performing surgical operations or in examining syphilitic cases; persons have frequently been inoculated in the process of tattooing or vaccination when saliva or vaccine-lymph from diseased individuals was employed. Infection may be caused by kissing, or indirectly by the use of drinking-vessels which have been employed by the diseased. The newborn may be syphilitic in consequence of disease of the father or mother; and healthy wet-nurses may be infected by syphilitic nurslings. In addition to the specific cause, surrounding conditions and individual susceptibility doubtless play a part. During the Middle Ages this disease at times and in certain places almost attained the character of a universal scourge. Its manifestations were severe, its course rapid, and in every sense its nature was malignant. Cases of this description are exceedingly rare at the present day.

Pathological Anatomy.—The pathological course of this disease may be divided into three stages: the *initial*, the *secondary*, and the *tertiary*. The disease may abort at any stage, but such an occurrence is rare. Not infrequently, especially in women, the first and even the second stage as well may be overlooked.

Chancre.—In the initial stage there is formed at the point of inoculation a primary lesion, commonly termed "chancre." This may make its appearance first as a somewhat red and inflamed papule, or as a vesicle which ruptures and thus produces an erosion. When it begins as a papule the surface soon becomes eroded, and thus a superficial ulceration is established. The peculiar feature of this lesion, to which Hunter called particular attention, is its hardness or induration, and it is by this feature largely that it is distinguished from the soft chancre or chancroid. The initial or primary lesion may remain indolent or as a small erosion for a long time, or it may soon cicatrize and leave a more or less definite scar. The chancre occurs upon the glans penis or prepuce, or within the urethra of the male; and in the vagina, urethra, or upon the cervix uteri and external genitalia of the female. Extragenital chancres may be observed in the rectum or anus, on the lips or tongue, tonsils or pharynx, the fingers, or other parts.

Secondary Lesions.—At the end of a variable period of time after the eruption of the initial sore secondary manifestations of the disease make their appearance. The spread at first follows the lymph-channels, but when once the infiltrative lesions of the blood-vessels begin, as in late primary syphilis, the dissemination is by the blood-stream. The first secondary lesions, as a rule, are swelling and induration of the neighboring lymphatic glands (*syphilitic bubo*). Later the superficial lymph-glands of the entire body become swollen and, like those in the neighborhood of the lesion, indurated. At the same time eruptions upon the skin

and mucous membranes make their appearance. The interval between the primary and the secondary manifestations is variable. Sometimes it is but a few weeks (three or four), at other times it may be several months. The manifestations of the secondary stage may begin with fever and constitutional symptoms, suggesting sudden and recent infection, and at the same time changes in the blood (rapid reduction of red corpuscles, moderate leukocytosis) make their appearance. Among the *lesions of the skin* various forms of papules, macules, and scaly eruptions are most frequent and characteristic. The lesions are usually symmetrically arranged on the two sides of the body and cause but little irritation. The color of the skin is frequently said to be somewhat coppery. On the mucous membranes and neighboring skin the most characteristic lesion of this stage is the *condyloma latum*, or *mucous patch*. This appears as a somewhat elevated patch with superficial erosion or ulceration. The surface has a necrotic appearance and may be covered with more or less secretion.



Fig. 119.—Gummata of the liver.

Tertiary Lesions.—These may take the form of ordinary inflammatory changes of the mucous membranes or of other parts, with a pronounced tendency to fibrous-tissue overgrowth and thickening, or of definite nodules—the syphilitic *gummata*, or *syphilomata*. Among the diffuse syphilitic changes of the tertiary stage may be ranked nodular thickening of the intima of the blood-vessels, certain changes in the liver, spleen, kidneys, and heart muscle, and also similar alterations in the nervous system.

The localized lesions of the tertiary stage—the gummata—are most frequent in the bones (tibia, sternum, and skull); and in the internal organs, such as the liver, lungs, kidneys, heart, and brain.

The gumma presents itself as a nodular mass, varying in size from small tubercle-like formations (miliary gummata) to tumors the size of an orange or larger (Fig. 119). It is hard, and has frequently an elastic character, which has suggested the name “gummy tumor” or

“gumma.” On section, the substance is frequently found to be gelatinous or mucoid in appearance; but there is nearly always considerable induration, either peripheral, in the form of a capsular enclosure, or striate, in the form of bands extending from the center to the periphery and into the surrounding tissue. Occasionally gummata soften very rapidly and become converted more or less completely into puriform collections. When situated in the mucous membranes or adjacent to the surfaces of the body, suppurative, fatty, or necrotic softening may lead to the formation of superficial ulcerations. These may remain indolent or may gradually become cicatrized. Sometimes a gummatus lesion disappears entirely by absorption without leaving a trace of its existence.

The histology of syphilis is given on p. 145, among the specific infections, so that it is only necessary here to review the general features of the pathologic anatomy. The primary effect of the invasion of the spirochete is to injure the cells and incite round- and tissue-cell proliferation, followed by fluid and connective-tissue cell increase. The blood-vessels are attacked early and the spirochete characteristically excites endothelioid increase in all of the coats. The intimal changes are obstructive, leading to anemia and connective tissue replacement both in the vessel itself and the tissues supplied by it. The central necrosis of gumma is doubtless due to this. The fibrosis is largely due to the prolonged irritative effect of the spirals and to the debris of cellular destruction. Scars of considerable size are formed in the liver, brain, kidneys, etc., by the excessive scar tissue. The spirochetes seem to prefer those places where blood-supply and cellular activity are greatest, such as the bone-forming layer of the peritoneum and epiphysis and the sinusoids of the liver. Amyloid disease is frequently seen as the result of syphilis.

Parasyphilis is a name given by Fournier to certain diseases, chiefly of the nervous system, in the clinical history of which syphilis is practically always noted. The pathological lesions are similar but not identical with those of syphilis, and some have doubted their luetic nature. Noguchi has lately found the *Spirochæta pallida* in the brain of paresis, a discovery which leaves hardly any doubt as to the syphilitic nature of this condition. He has, moreover, produced lesions in rabbits by injecting the brain of paretics.

Pathological Physiology.—Syphilis is one of the most persistent of the infectious diseases, and occasions widespread changes that are doubtless toxic in character. The nature of the toxic principles, however, is entirely unknown. In the tertiary stage pronounced anemia (cachexia) is frequent; and in the secondary stage rapid chloro-anemia with leukocytosis is quite common.

Congenital Syphilis

Syphilitic lesions may be found in the newborn or may develop some time after birth. *Spirochæta pallida* and histological changes

of syphilis have been found in the placenta. Not rarely they occur in the newborn fetus and cause its premature death. Frequently there is maceration of the fetus prior to expulsion. The infection is in the ovum when the mother is infected before conception, and in the placenta when infection occurs during pregnancy. Among the lesions observed, sclerotic changes in the lungs, liver, spleen, pancreas, and other organs are conspicuous; and a certain condition of the bones is quite characteristic. The latter consists of a hyperplasia of connective tissue and fatty degeneration at the junction of the epiphyses of the long bones with the shafts. Various superficial lesions of the skin in the form of vesicles or bullæ, fissures, and the like may be observed. The blood may present considerable excess in the number of leukocytes. An almost distinctive condition of second dentition is that known as Hutchinson's teeth. This consists of a notched indentation of the cutting surface of the upper central incisors. In addition, the teeth are often wedge



Fig. 120.—Hutchinson's teeth.

shaped and peg-like (Fig. 120). All cases of inherited syphilis do not present this condition, and it occasionally occurs in non-syphilitic children.

RELAPSING FEVER

Definition.—Relapsing fever, or typhus recurrens, is an infectious disease caused by a specific organism which is found in the blood.

There are four varieties, depending upon the biology of the spirochete concerned, but differing very little clinically:

European relapsing fever, *Spirochæta obermeieri*; African relapsing fever, *Spirochæta duttoni*, transmitted by the tick *Ornithodoros moubata*; American relapsing fever, *Spirochæta novyi*; Bombay relapsing fever, *Spirochæta carteri*.

The transmission of the first, third, and fourth is not known, but is probably due to some tick. Nicolle's result would indicate that the human form may be transmitted mechanically by the louse, but not by the biting of this parasite. *Spirochæta obermeieri* is described as the type. Opinion is still divided as to the proper classification.

Etiology.—The *Spirochæta obermeieri* is a flexible spiral organism with six to twenty curves, in length several times the width of the red corpuscle (16 to 40 μ). It is found in the fresh blood, and presents active corkscrew, serpentine, and vibratory movements due to rotation and a flagellum-like extremity (Fig. 121). Recently it has been claimed by Schaudinn that this and other spirochetes belong to the group of *flagellates* (animal parasites) and are closely related to the *trypanosomes*. Novy's investigations appear to have completely disproved this view.

The organism stains well with ordinary anilin dyes, but not by Gram's. The relation of this spirillum to the disease can hardly be questioned, as it is invariably present and appears in the blood during the paroxysms

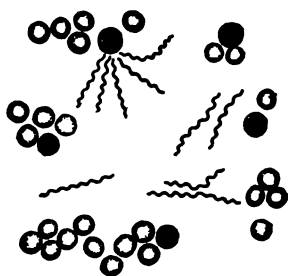


Fig. 121.—*Spirochæta obermeieri* in the blood (von Jaksch).

of fever and disappears in the intervals, thus showing its relation to the symptoms of the disease. In the case of *Spirillum duttoni* the female tick bites, becomes infective in a week, remains so all its life, and transmits the virus to the young. All forms have now been cultivated by Noguchi in anaërobic cultures of defibrinated patient's blood in ascitic fluid agar to which fresh tissue has been added. They breed true to type. The spirochetes may be transformed to mice and monkeys. They are numerous in the blood during the fever, but rapidly disappear at the crises, due to the presence of

a spirochetolytic substance in the blood. Immune bodies also appear and can be used to impart passive immunity to other animals.

Pathological Anatomy.—The spleen becomes greatly enlarged; it frequently presents a variegated appearance on section, due to areas of anemic infarction and necrosis, or fatty degeneration alternating with deeply congested portions. The spirochetes can be found in this organ, particularly in cells. The lymphatic tissues are swollen throughout the body.

Pathological Physiology.—The peculiar feature of relapsing fever, the one that has given it its name, is the recurring paroxysms of fever. The cause of this periodicity is as yet unknown, though it is likely that the development of the spirochete is such as to determine the relapses.

VINCENT'S ANGINA

This is an acute infectious, pseudomembranous and ulcerative form of pharyngitis and tonsillitis giving a grayish or greenish exudate. The process below the membrane is usually necrotizing and spreading, and may persist for a long time. There are constitutional symptoms and involvement of the regional lymph-glands. The organism of the disease is found in two forms, the *Bacillus fusiformis* and the *Spirillum vincenti*. They are believed to be two forms of the same organism, as the spiral has been said to grow from the rod. The rod is irregularly staining and pointed, 3 to 12 μ long by 0.3 to 0.8 μ wide. The spiral is long, wavy, uniformly staining, flexible, and has pointed ends. The rod forms spores. The organisms are anaërobic, growing best upon ascitic fluid agar, on which they appear as minute gray colonies. Gas is formed in glucose media. Cultures have a fetid odor. The pathogenesis of the organism for lower animals is practically nil; no immunity reactions are known (Fig. 122).

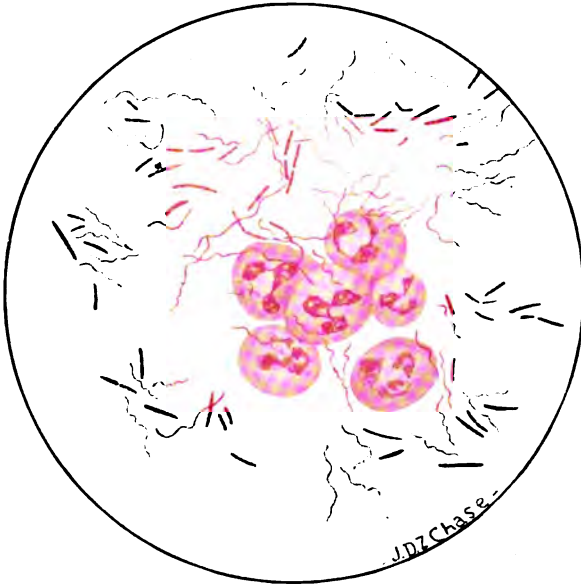


Fig. 122.—The fusiform rods and spirilla of Vincent's angina. Smear direct from throat.

FRAMBESIA OR YAWS

This is a tropical disease resembling syphilis in its primary indurated sore and secondary rash, caused by a spirochete (*Spirochaeta pertenui* Castellani), similar to the *Spirochaeta pallida*. The eruption is yellowish, papular, covered with crusts, and consists histologically of epithelial hyperplasia, in the form of papillomatous growths or extensions downward, associated with increase of leukocytes, plasma, and eosinophile cells. The disease tends toward recovery, except in children and debilitated persons. The productive character of the lesions is not so marked as in lues. The disease has been transmitted to monkeys.

DISEASES DUE TO HIGHER BACTERIA

ACTINOMYCOSIS

Definition.—A tinomycosis is a chronic infectious process characterized by inflammatory reaction of the tissues with a tendency to the formation of suppurative foci, and due to the specific action of a micro-organism, the *Actinomyces bovis*.

Etiology.—Actinomycosis is a disease of cattle, horses, swine, sheep, the llama, the elephant, deer, dog, and occasionally of man.

The specific cause of the disease is an organism which occurs in the tissues in the form of clusters having a radiate structure, and it has, therefore, been termed the "ray fungus." These clusters may be so small as to be invisible to the naked eye, or they may reach considerable dimensions by their growth and aggregation. The central part of the

cluster frequently has a granular appearance, suggesting a mass of micrococci. Reaching out from this may be seen more or less regularly diverging striæ or rays, and the periphery is composed of what appear to be bulbous extremities of the rays (Fig. 123).

Bostroem, in 1890, and Wolff and Israel, in 1891, published notable articles on actinomycosis and respectively isolated an aërobic and an anaërobic growth. The relation of the former to actinomycosis has, however, been disproved, while the anaërobic growth alone is important.

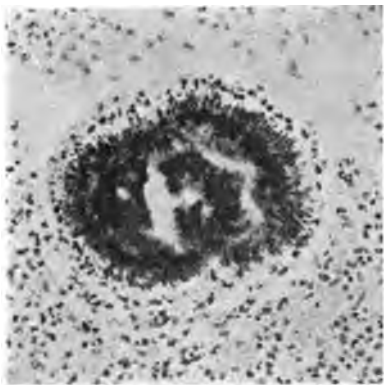


Fig. 123.—Actinomyces cluster (Karg and Schmorl).

The aërobe of Bostroem was apparently a contaminating organism related to the branching organisms which occur in the outer world, and that have been variously classified as streptothrix, cladothrix, etc. As these occur on various grains and on the spears of the oat seed, etc., Bostroem believed that the organism was derived from such sources. More recently accurate studies like those of Wright (*Jour. Med. Research*, May, 1905) seem to have disproved the connection of the aërobic organism and to have established the independence of the true actinomyces from the group of branching

organisms referred to. Wright insists that these should be classified as a separate genus under the name of *Nocardia*.

Cultivation of the Organism.—Growths have been obtained upon sugar-agar, in bouillon, and various other media. Suspension cultures in dextrose or glucose sugar show in the course of two to four days scattered colonies in the depth of the agar and a very few within 5 to 10 mm. of the surface. A shallow zone of closely set colonies giving the appearance of a dense cloudiness in the media and about 2 to 4 mm. wide is generally found at a point about 5 to 10 mm. below the surface. Below this zone the colonies are more scattered.

The growths are essentially anaërobic, and grow best at body temperature. Under the microscope the smaller colonies are found to be spherical masses of branching filaments radiating from the center. The branching is true branching and increases as the colony grows older.

In stab-cultures in sugar-agar the growth appears as a dense gray streak or line of small nodules in the deeper parts of the stab. No growth occurs near the surface.

In bouillon, solid white masses form at the bottom of the tube; none appear near the surface. In bouillon the growths occur both under aërobic and anaërobic conditions, but in the case of the former Wright suggests that on account of the compactness of the masses there are really anaërobic conditions within the colony.

While this anaërobic organism may be the most important one in

actinomycosis, an aërobic growth has been cultivated, and it seems that both forms may cause the disease.

The cultivation of these organisms presents unusual difficulties, owing chiefly to the frequent presence of other bacteria in the lesions, which usually grow more rapidly and more luxuriantly than does the specific organism.

In a few cases pure cultures were obtained by planting the granules directly in bouillon. In some instances of contamination, by allowing the tube to stand for several days, the contaminating organisms died out and transplants then yielded pure cultures. Generally sugar-agar was the medium employed for isolation of the micro-organism. It grew well only in agar and bouillon cultures and in the incubator at 37° C. (98.6° F.). In the other usual cultural media and at room temperature it grew very poorly or not at all. It was essentially an anaërobe, and did not form spore-like reproductive elements. In cultures its colonies were similar in character to those in the lesions. The vitality of the micro-organism was variable. In general, it did not seem to survive as long in cultures as when dried on the sides of test-tubes. It was killed by exposure to a temperature of from 60° to 64° C. (140°–147.2° F.) for ten minutes. The micro-organism stained well by Gram's method, the clubs losing the stain and taking the contrast stain; it is not acid fast to Gabbet's decolorizing solution after staining with carbol-fuchsin.

The filaments of colonies immersed in animal fluids, such as blood-serum and serous pleuritic fluid, may under certain unknown conditions become invested with a layer of hyaline eosin-staining material of varying thickness and the filament may then disappear. Thus structures are produced that seem to be identical with the characteristic "clubs" of actinomyces colonies in the lesions.

Pathogenicity.—Inoculation experiments on animals with cultures of the micro-organism result in producing in the tissues of the inoculated animal characteristic "club"-bearing colonies. This club formation Wright is inclined to believe represents a kind of protective membrane for the mass of the colony against the destructive action of the juices and cells of the tissue. After the inoculation of animals nodular lesions and in some instances relatively extensive lesions were produced. They, however, showed little tendency to progress and only in a few cases did multiplication of the organism in the body of the animal seem probable. In other words, these results simulate closely the negative or ambiguous results obtained by other observers who inoculated animals with the lesions of actinomycosis. It would seem, therefore, probable that the micro-organism in the cultures was identical with the micro-organism in the lesions.

Wright recognized but one micro-organism as the characteristic infectious agent in typical actinomycosis, and applies to it the generic and specific name of *Actinomyces bovis*, as given by Bollinger and Harz. There is not sufficient difference between the actinomyces from the human and bovine cases to justify their classification as separate species.

The manner of infection with the actinomyces is not completely

determined. Formerly it was thought that the parasite was carried to the tissues by various vegetable substances, particularly the spears of the oat-seed and other grains. Sometimes these have been found embedded in the lesions; in other cases splinters of wood have been discovered. The fact that the organism prefers anaërobiosis and grows



Fig. 124.—Actinomycosis of the jaw-bone of an ox. The dark areas and the broken-down part in the center of the picture are foci of the disease. The whole bone is enlarged.

only at body temperature tends to disprove this view, and it is likely that the actinomyces is a normal inhabitant of the mouth and gastrointestinal tract and always derived from these sources, although, of course, infection by infected grain or communication with infected animals or persons can transmit the disease. Carious teeth and lesions of the mucous membranes may play a part in the etiology.

Pathological Anatomy.—The pathological changes induced by the actinomyces consist of round-celled infiltration and proliferative changes in the connective tissue surrounding the parasite, and sometimes secondary softening, necrosis, or suppuration. The granulation tissue of actinomycosis is especially rich in leukocytes, and not infrequently these form dense foci, which later develop purulent collections. In cattle the disease affects the lower jaw, less frequently the upper jaw or other bones; the tissues of the neck, the tongue, and other parts. In man it is met with in the gums, the cheeks, and floor of the mouth; in the lungs, intestines, and other internal organs. The naked-eye appearance of the lesions may first be simply that of a hard red papular formation, with more or less induration surrounding it; later this tends to increase in size and may break down, forming necrotic or suppurative excavations. The process of repair or cicatrization may proceed in some parts to the extent of almost complete repair, while the suppurative or necrotic change advances in other directions, and thus cavities and irregular communicating sinuses are established. The part in which the disease exists may be considerably disfigured and much enlarged. The pus or necrotic material within the lesions contains peculiar granular bodies, the "sulphur granules" or actinomycosis bodies. The sand-like or sulphur granules measure 0.2 to 0.6 to at times 1.2 mm. They are of a gray, yellow, green, to red color; when young, soft; when older, much tougher in consistency. Occasionally calcification of the diseased area may take place. When the jaw-bone is affected the disease, as a rule, begins about carious teeth, fistulæ communicating with the roots of teeth (Fig. 124).

In the case of disease of the lungs some have observed a preliminary catarrhal inflammation of the bronchi. More frequently, however, there are from the first nodular areas of bronchopneumonia, which tend to undergo changes similar to those already described. The surrounding lung tissue frequently becomes indurated from interstitial pneumonitis. Extension may occur to the pleura, pericardium, and mediastinal tissues.

In the case of actinomycosis of the intestinal tract there are first elevations of the mucous membrane, the disease involving the mucosa and the submucosa. Subsequent softening of these leads to the formation of ulcerations. Extension to the peritoneum and to the other organs of the abdomen may take place.

In any case of actinomycosis a penetration of the blood-vessels or lymph-channels may lead to metastases. Thus in actinomycosis of the abdominal cavity the liver is frequently involved; and other parts of the body may be similarly affected. Actinomycotic lesions of the brain (abscesses) are sometimes seen in such instances. In other cases of cerebral involvement there may be no evidence of the original focus or point of entrance of the germ.

Microscopically, the characteristic feature of this disease is the parasite itself surrounded by lymphoid cells in considerable numbers, with some epithelioid cells and occasionally giant cells. When the

process tends to a favorable termination by cicatrization, fibrous-tissue formation proceeds in the usual manner.

Pathological Physiology.—The actinomyces is mainly active as a local parasite, the general disturbances of health being comparatively slight. There is a marked tendency to limitation or retardation of the disease, and sometimes this is effected completely.

MYCETOMA

Mycetoma, or madura-foot, is an infectious disease occurring in India and elsewhere, and probably caused by several organisms, certainly two, grouped under the name *Streptothrix* or *Actinomyces maduræ*. Babes asserts that the black variety is due to a mucor or aspergillus. The disease is not infrequent in Madura, Delhi, and other parts of India, and has been observed in Africa, southern Europe, and America.

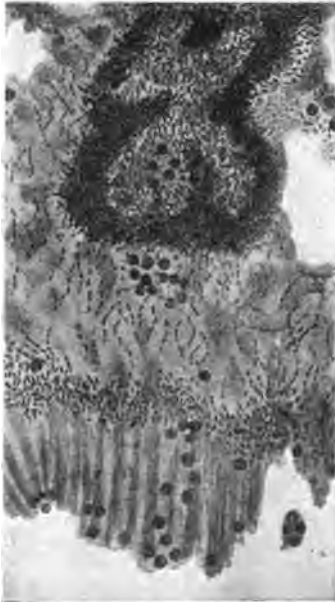


Fig. 125.—*Streptothrix maduræ* in a section of diseased tissue (Vincent).

Etiology and Pathological Anatomy.—As its name indicates, the disease affects the foot, and usually follows injuries, particularly thorn wounds. In rare cases the hands or other parts are affected. At first there is nodular inflammatory swelling, beginning on the plantar surface or dorsum of the foot and spreading to the sides. These swellings are hard and painless. Later, softening occurs and rupture takes place. Thin, watery pus is discharged, and this contains grayish or reddish granular bodies or black granules resembling particles of gunpowder. In the former case the term "pale mycetoma" is applied; the latter variety is called black or melanoid. In the later stages of the disease discharging sinuses may remain, while newer nodules, in turn, are formed and soften. Finally, the member af-

ected becomes greatly deformed, the portions not involved growing thin, while the diseased part increases in size. Death occurs from exhaustion or complications.

Histologically, the nodules resemble large tubercles, but are highly vascular. The bulk of the growth consists of granulation tissue cells, those in the center being small, those near the outer edge often large and containing two or more nuclei. True giant cells are rare. In the center may be found a branching micro-organism, called *Streptothrix maduræ* (Vincent). This stains by Gram's method, and sometimes shows somewhat bulbous swelling of the ends of the threads and their branches (Fig. 125). The mycelia of the black variety of mycetoma are described

by Laveran as thicker and coarser than those of the pale form, and he believes the organisms are of a distinct variety or species. Around the organism may be seen an area of degeneration, having a striate arrangement suggesting that seen in actinomycosis. Extensive degeneration and pus formation occur in the center of the diseased areas in the later stages; and hemorrhage may occur from the new blood-vessels. Histological examination of the granules in the pus shows the micro-organisms in the form of interlacing threads. Bodies resembling spores have occasionally been described.

The organism has not as yet been definitely classified. It is certainly allied with the actinomyces, but probably not identical. It has been cultivated upon various media, particularly infusions of hay and the like, rendered slightly acid in reaction. It forms small nodular and hard growths, which become rose-red in color when they cling to the sides of the test-tube near the surface of the liquid, or brownish when they sink to the bottom. Upon agar isolated grayish or, later, rose-red clusters are formed. Inoculation experiments have thus far met with little success. Local reaction has been so produced, but not a definite disease. Several investigators have reached the conclusion that there are two or more kinds of micro-organisms that have an etiological relation to cases of Madura foot. It has in particular been suggested that the white and black varieties of the disease have a distinct bacteriology. These views need further confirmation.

THRUSH

This condition occurs in newborn infants and in older children or adults who have become weakened by disease. The organism called *Oidium albicans* is a budding fungus, though some believe it a form of mould. If some of the milky deposits on the mucous membrane of the mouth which characterize the disease be removed and examined microscopically, mycelial threads and conidia are observed. The organism may be cultivated upon gelatin plates, in the form of whitish colonies on the surface, or granules with radiating processes in the depth of the medium. On potato and on bread it forms a white coating. The organism is present in the air and in various articles of food, so that infection readily takes place.



Fig. 126.—Thrush fungus (*Endomyces albicans*) (Kolle and Wassermann).

The organisms first grow upon the surface of the mucosa, but later may penetrate to considerable depth, and may attack blood-vessels. If this occurs, metastasis may result, with abscesses in different organs, notably brain and kidney.

SACCHAROMYCOSIS OR BLASTOMYCOSIS

This is a subacute infection, chiefly of the skin, caused by forms of yeast, *Saccharomyces hominis* or *S. busse*. There are probably several different species capable of setting up infection, but their action is essentially the same. *Saccharomyces tumefaciens* and *Blastomyces dermatitidis* are also names given to yeasts causing disease in the skin.

The yeast is a rounded or elongated (up to $30\ \mu$), doubly contoured, highly refractile body, with vacuolated, granular or clear cytoplasm; multiplication occurs by budding. The organisms are best stained by polychrome methods. They grow with difficulty and require carbohydrates. They are most easily obtained by inoculating guinea-pigs under the skin and culturing the pus. They produce an active cellular

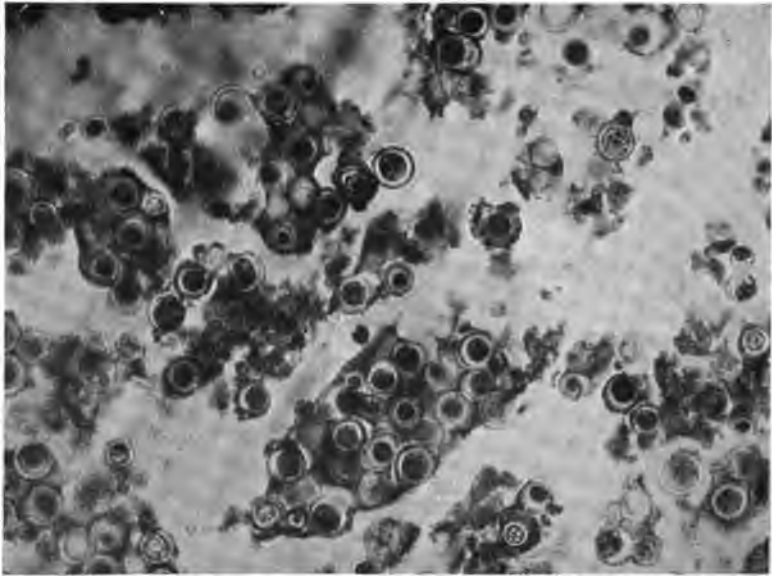


Fig. 127.—*Blastomyces* in pneumonic exudate (from a photograph by Dr. S. S. Kneass).

exudate in which fibrin is abundant. Necrosis is common. A toxin of moderate potency is produced. The lesions are said to be primarily cutaneous or pulmonary, although some question the latter. The spread is probably hematogenic, as scattered abscesses and osteomyelitis may occur. The lesion is usually a mixture of suppuration and granulation tissue (see p. 148). The disease may be transferred to the lower animals. No immunity reactions are of value.

Coccidiosis, or Oidiomycosis, is an acute infection due to the *Coccidioides immitis*, an organism closely related to the *Oidia*, and has some of the characters of both the classes, *Blastomyces* and *Hyphomyces*. It is a doubly refractile circular body in the tissue, occasionally growing out into mycelia, and always doing this in cultures. It develops by intracellular sporulation and not by budding. The infection usually

has its seat in the skin, but may become generalized. The lesion resembles a tubercle in the cellular and degenerative characters. Eosinophiles may be present.

Sporothricosis.—This is a disease consisting of cutaneous eruptions and multiple abscesses, usually in the skin, but not infrequently in the mucous membranes, muscles, tendons, and mammary gland. It is caused by the *Sporothrix beurmannii*, after the investigator who first accurately described it. The organism appears in several slightly different varieties. It occurs in lesions as round or oval yeast-like bodies, but on cultivation shows long mycelial threads from which grow yeast-like spores or gonidia. The spore body measures 3 to 6 by 2 to 4 μ . In the tissues usually only the yeast-like stage is seen, but short mycelia may form. The organism is aërobic and requires the presence of carbohydrate for its growth. The disease is subacute. In addition to the above-mentioned lesions, the mould may produce a nodular lymphangitis in man as it can in the lower animals. A disseminated form with the moulds in the blood is reported and considered a grave condition. The disease is transmissible to the lower animals. The blood contains an agglutinin and a complement-fixing body against the mould. For histology of the lesions, see p. 149.

Dermatomycosis.—Besides the above infections, there are several moulds which infest the skin and produce more or less specific reactions of clinical rather than pathological importance. The following skin diseases are included under this heading: Favus, caused by *Achorion schönleinii*; ringworm, including *Tinea tonsurans*, *Tinea sycosis*, *Tinea circinata*, and *Tinea versicolor*, due to varieties of the genus of moulds *Trichophyton*. The moulds infest the epidermis or penetrate the gland ducts. Their action is to cause the epithelium to degenerate and desquamate, while a round and polynuclear cell invasion occurs in the dermis. There is little specificity pathologically.

Granuloma pyogenicum, or human botryomycosis, is a granulating pyogenic and ulcerative condition of the dermis, penetrating to the surface, said by some to be due to bacteria, but lately ascribed by others to an intracellular protozoön-like body.

OTHER BACTERIA NOT CAUSING SPECIFIC INFECTION

THE HEMORRHAGIC DISEASES

These diseases constitute a group of affections of probably quite divergent character, which, however, are similar in presenting hemorrhages in and from the mucous membranes, in the skin, serous surfaces, and in the deeper tissues or organs.

The general causes of hemorrhage must be considered in connection with these diseases. Among the causes capable of producing hemorrhages such as occur in the hemorrhagic diseases are *mechanical conditions*, as atheroma or other diseases of the walls of the blood-vessels; *toxic conditions*, such as poisoning by the venom of animals and by various blood-poisons, and probably obscure poisons produced in the

course of anemia or other diseases; *infectious conditions*, such as occur in hemorrhagic variola, scarlatina, etc.; and *nervous conditions*, as are illustrated in the hemorrhages following injuries to the brain and those accompanying certain states of cerebral excitation.

Clinically, the hemorrhagic diseases or *purpuras* may be classified as *primary* and *secondary*, the former occurring without any definite preceding disease; the latter being symptomatic of various disorders. Among the primary there are: (1) *infectious forms*, including, with more or less probability, purpura, scurvy, and various forms of cryptogenetic sepsis; (2) *toxic forms*, as those due to drugs and venom of animals; (3) *mechanical forms*, as, perhaps, *hemophilia*, to the extent that vascular weakness may be a factor. Among the secondary purpuras are: (1) *infectious forms*, as scarlatina, variola and the like; (2) *mechanical forms*, as those due to cardiac and arterial diseases, or embolism; (3) *toxic forms*, as those resulting from intestinal auto-intoxications, jaundice, pernicious anemia, etc.; and (4) *nervous forms*, as those due to hysteria, diseases of the brain, etc.

The underlying conditions in cases of infection whose most important manifestation is hemorrhage are to be sought first in the blood-vessels and then in the blood. In the former case the poison has a deleterious effect upon the permeability of the blood-vessels, while in the latter hemolysis occurs in the blood-stream; thus escape is easy. It is probable that the two actions are to be found in all hemorrhagic conditions.

The infectious purpuras interest us particularly in the present place. Various micro-organisms have been found in different forms of hemorrhagic disease. Kolb described a bacillus pathogenic for animals which occurred in 5 cases of hemorrhagic purpura. Babes and Oprescu isolated a bacillus from one case of hemorrhagic septicemia, and others have found various micrococci, especially the streptococcus. It is not unlikely that various micro-organisms may assume a peculiar virulence and acquire the power to produce hemorrhages under certain circumstances.

Some recent investigations seem to indicate that scurvy is a toxemia due to poisons generated in preserved meat foods as a result of autolysis. In scurvy, however, several micro-organisms have been described, but the one which has the best claim for consideration is that discovered by Babes, a delicate bacillus occurring in the gums. Streptococci were found in association with it. Some Japanese investigators have recently claimed to have discovered a specific bacillus in the blood and viscera, agglutinable by the serum of scorbutic patients. Present indications, however, do not very strongly substantiate the probability of a bacterial cause for this disease.

PROTEUS INFECTION

The *Bacillus proteus* and its several subvarieties occur in decomposing animal matter and in association with necrotic and gangrenous

processes in the living body. The organism is a small, motile bacillus, occurring in pairs and less often in chain formations. It is abundantly supplied with flagella.

Cultivation and Demonstration.—The organism grows very well at ordinary temperatures, and forms characteristic growths on gelatin-plates. At first yellowish colonies with outgrowths are formed; the gelatin liquefies, and the outgrowths move about in a tortuous manner and become separated from the original growth. Peculiar figures are formed, and the term *Bacillus figurans* has been applied. The cultures have a putrid odor. The organism is readily stained with ordinary solutions like carbol-fuchsin.

Pathogenicity.—Injected intravenously in animals, hemorrhagic vomiting and diarrhea result. In man the bacillus has been found associated with phlegmonous inflammations, gangrenous processes, cystitis, pyelitis, and in infectious icterus (Weil's disease). It is sometimes the cause of meat poisoning.

INFECTIOUS DISEASES WHOSE CAUSE IS NOT CERTAINLY KNOWN. FILTERABLE VIRUSES

YELLOW FEVER

Definition.—Yellow fever, or typhus icteroides, is now recognized as infectious and transmissible through the bite of a certain form of mosquito, the *Stegomyia fasciata* or *calopus*. The specific organism has not been identified.

Etiology.—Many different organisms have been described as the cause of yellow fever, most prominent of them being the *Bacillus icteroides* of Sanarelli. It seems now that none of the many is of any importance whatever, as the disease is transmitted by mosquitoes in which no bacillary form of infective agent has been found, and because the virus is filterable.

The Rôle of Mosquitoes.—The experiments of Reed, Carroll, and Agramonte demonstrated the importance of mosquitoes as agents in the transmission of the disease. It was definitely proved by Reed and his associates that a special form of mosquito, the *Stegomyia fasciata*, carries the contagion from one person to another. The germ must pass a certain incubation period in the body of the mosquito, as the bite of the latter is not found to cause infection until after an interval of twelve days or more from the time it has fed on the yellow-fever patient. A bite at an earlier period after contamination did not confer immunity against a subsequent attack of the disease. This indicates that a cycle of development must occur in the mosquito. Without the *Stegomyia fasciata* there can be no yellow fever, as there can be no malaria without *Anopheles*. The mosquito must feed on a yellow-fever patient during the first three days of the fever, and after the twelve-day period is infective for at least fifty-seven days. The spread of the disease is checked by preventing the mosquito from biting patients or by its whole-

sale destruction. The blood of patients is infective even after passage through a Berkefeld filter. One attack confers immunity. Experiments were conducted directly on non-immune volunteers, and the transmissibility of the disease was positively proved. The incubation period of the disease, the time elapsing from the time of the mosquito's bite up to the first definite symptoms, varied from forty-one hours to five days and seventeen hours. The results of the practical measures of quarantine instituted at Havana in accordance with Reed's work—destruction of all mosquitoes and careful exclusion of mosquitoes from the patients, with entire disregard of clothing, bedding, etc.—show that the disease is not directly contagious. Non-immune nurses attend yellow-fever patients with impunity. The disease can also be transmitted experimentally by subcutaneous injections of blood taken from patients in the first and second days of the disease, which proves the presence of the parasite, in the blood at least, in the earlier stages of the disease. The passage of the parasite through an intermediary host is, therefore, not essential. In this respect yellow fever resembles malaria.

Pathological Anatomy.—The lesions of this disease are mainly those of the internal organs—liver and kidneys. In the liver extensive fatty degeneration leads to swelling and light color of the organ, and on section there may be a mottled appearance due to the alternation of healthy and fatty areas. In the kidneys degenerative changes of the parenchyma and extravasation of blood are associated in varying proportions. The appearance may be that of an acute hemorrhagic nephritis or, more particularly, that of degenerative nephritis. Hemorrhages in the mucous and serous surfaces are frequent, particularly extravasations in the mucosa of the stomach.

Pathological Physiology.—The organism of yellow fever probably produces abundant toxin.

MEASLES¹

Measles, or rubeola, is an infectious and contagious disease, in all probability due to some micro-organism. A number of micro-organisms have been described. Several observers (Canon and Pielicke, Czajkowski) have found a bacillus somewhat resembling that of influenza; others have found bacilli resembling the pseudodiphtheria bacil-

¹ Certain investigators have discovered bodies having some of the appearances of protozoa in measles, scarlet fever, pernicious anemia, leukemia, sarcomata of various sorts, and in a number of other diseases. These observations, however, do not merit further discussion in this place. Future investigations must decide whether they have been accurate or not.

Mallory (*Jour. Med. Res.*, January, 1904) found in the skin of 4 cases of scarlet fever, dying in the early stages of the disease, certain bodies which in their morphology suggest that they may be various stages in the developmental cycle of a protozoön. They were found once in small numbers in the epidermis of the tongue. They were not present in the skin of 6 cases dying in the early stages of the disease, nor in a number examined in the desquamative stage. They occur in and between the epithelial cells of the epidermis, and free in the superficial lymph-vessels and spaces of the corium.

There are in addition to these forms larger coarsely reticulated forms which may represent stages in sporogony or degenerations of the other forms.

The name *Cyclasterion scarlatinale* has been proposed by Mallory for this organism. These and other protozoön-like bodies, such as described by Doehle, Ross, and others, are now considered by many writers as belonging to the Chlamydozoa.

lus, but the bacteriology is still unsettled. Doehle described a protozoan organism occurring in the blood. Hektoen has inoculated healthy persons with the blood from cases of measles and has demonstrated the transmissibility.

The disease is at present regarded as due to an ultramicroscopic virus which will pass through a porcelain filter. The virus is present in the blood, buccal and nasal secretions, and can be transmitted to monkeys, in which it produces an atypical infection. It may be found in the blood before the Koplik spots or eruption appear. It has not been cultivated.

Mild catarrhal inflammations of the faucial, nasal, and conjunctival membranes and of the bronchial mucosa are customary lesions. With these conditions is associated some congestive and inflammatory enlargement of the regional lymphatic glands. In severe cases pseudomembranous inflammations of the throat are sometimes met with, and bronchopneumonia and parenchymatous nephritis are occasional complications. The eruption of the skin is the visible evidence of a moderate dermal and subdermal inflammation. Focal necroses of the liver have been described. Many of the lesions are doubtless caused by secondary infections.

SCARLET FEVER

Scarlet fever, or scarlatina, is an infectious and contagious disease probably due to a micro-organism. A variety of organisms have been discovered in cases of scarlet fever, but none as yet has proved to be specific. Among other bacteria the pyogenic micrococci (streptococci) have been regarded as etiological agents. This, however, is by no means established. Protozoan organisms have also been described (Doehle). Mallory has described under the name of *Cyclasterion scarlatinale*¹ structures which present the appearance of protozoa.

The virus is now believed to be filterable and ultramicroscopical. An atypical infection is produced in monkeys by injection of a patient's blood during the height of the attack. The claim that scarlatina is due to streptococci or to the leukocyte inclusion bodies of Doehle cannot be substantiated.

Lesions of the mucous membranes and glands similar to those of measles, but usually more intense, are generally present. Suppuration of the glands of the neck is a possible termination, and severe inflammations of the throat, middle ear, larynx, and trachea, with endocarditis or pericarditis, are much more frequent than in measles. Many of these complicating conditions are caused by secondary infection with the *Streptococcus pyogenes*. Diphtheria (as contrasted with streptococcic lesions of the throat presenting a similar appearance) is not rare as a complication. Parenchymatous nephritis is a lesion of great clinical interest, while focal necroses of various organs are observed in fatal cases.

¹ See note, page 352.

MUMPS

The bacteriology of mumps is uncertain. Charrin and Capitan isolated a number of organisms, mainly micrococci and motile bacilli. A number of other authors subsequently obtained similarly indefinite results. Laveran and Catrin in 1893 found a diplococcus.

The pathology of mumps is that of an acute inflammation of the parotid or submaxillary gland. This rarely terminates in suppuration or, on recovery, in induration of the gland.

VARIOLA AND VACCINIA

A number of bacteria have been described from time to time in these diseases, and various micrococci in particular have been found in the pustules, but none of these can be considered as specific. Several bacilli, one form resembling the diphtheria bacillus, have been recently described.

In 1887 Pfeiffer and van der Loeff independently described a protozoan parasite of the order *Sporozoa*, which occurs in the cells of the rete. This organism was found in variola as well as in vaccinia. Pfeiffer, Guarnieri, and other investigators found that by inoculation of the cornea of rabbits large numbers of the supposed parasites make their appearance in the epithelial cells. These organisms are rounded bodies lying in the protoplasm of the cells, sometimes singly, sometimes in groups of two or three. Slow ameboid movements are visible and the organisms present one or more nuclei. Spore formation has been observed by several investigators. Guarnieri suggested the name *Cytoryctes variolæ seu vaccinæ*.

Councilman, Magrath, and Brinckerhoff in 1903 confirmed the findings of Guarnieri in 1892 and of Wasielewski some years later as to cell inclusions in lesions of vaccinia and variola. They look upon them as living organisms and the probable etiological factor of vaccinia and variola. In vaccinia the cytoryctes occurs as a structureless mass in the cytoplasm, where it is thought to undergo asexual division by breaking up into small round segments. In variola the parasite is said to invade the nucleus also, undergoing there segmentation into ring-like bodies; this is supposed to be the sexual phase.

The formation of the exanthem may be due to the infected endothelial cells of the capillaries or lymph-spaces being carried to the skin capillaries by the blood-current. No differential method of staining has as yet been offered. The nature and significance of these supposed organisms have not yet been positively determined. Some authorities, as Ewing, look upon them as products of cell degeneration. Lately the view has been defended that they are the *Chlamydozoa* of Prowaczek, probably due to a virus acting upon the chromatin, with lysis thereof.

Secondary infections with various micrococci or other organisms are common in small-pox and vaccination, and may play an important part in pustulation, and in the more definite complications, such as

septicemia, pneumonia, hemorrhagic septicemia, erysipelas, and the like.

Councilman, in discussing the relations of variola vera, vaccinia, and variola inoculata, points out that vaccinia differs from small-pox in three ways: first, the period of incubation is shorter, being five days in man and three days in calves, while that of variola is twelve days. Second, in vaccinia the general eruption is absent. Third, for the development of vaccinia the virus must be placed in contact with a susceptible epithelial surface, and cannot be carried by the air.

In his studies of 52 autopsies careful study was made to determine the existence of a primary variolus pustule from which the general infection might have occurred. None was found, nor are there any symptoms of such a primary lesion. Nevertheless, a simple pox, in the lungs, for instance, might occasion no distinctive signs. He believes that the infection passes through the air and enters the system through the lungs. The virus is filterable through porcelain in diluted condition.

Regarding immunity conferred by vaccination, he states that all the evidence goes to show that it is due to germicidal power of the blood-serum which enables the serum to destroy the virus of vaccinia and small-pox.

VARICELLA

The etiology of chicken-pox is even less definitely determined than that of small-pox. Pfeiffer discovered the same organism described by him in vaccinia and variola. Bacteria of one sort or another have been occasionally found.

TYPHUS FEVER

An acute epidemic disease attended with a fairly typical clinical course and macular eruption, supposed to be transmitted by the louse, *Pediculus vestimenti*. The virus is found best in the blood toward the end of the disease, is filterable, and may be transmitted to monkeys. Many different organisms have been discovered and described, but none are now believed to be the real cause. The organism now receiving most attention is a non-motile rod with a palely staining central area, circulating in the blood. It is said to grow feebly under anaërobic conditions if cultures are made between the sixth and ninth day of the attack. It will act as an antigen in the complement fixation series.

The severe typhus of Mexico is called "tabardillo." There is a mild infection called "Brill's disease," after the observer, believed to be a sporadic form of typhus. It has been observed among the Hebrews of New York and other American cities.

The lesions of typhus fever suggest an intense infection and intoxication. The blood is often dark-colored and rapidly putrifies. Various organs, such as the liver, kidneys, and heart, show pronounced cloudy swelling or fatty degeneration of the cells. The spleen is notably enlarged, often quite soft, and may present infarctions due to thrombus formation.

Inflammations of the mucous membranes, especially bronchitis, pharyngitis, and laryngitis, are common, and pneumonia is a frequent result.

RABIES

Etiology.—We have every reason to believe that rabies is due to a specific germ. In 1903 Negri described an organism which has received considerable recognition as the probable specific cause of the disease. The “Negri bodies” have been found in the large nerve-cells of the central nervous system, especially in the cornua ammonis, in various animals and human beings affected with rabies. They are absent in other conditions. In early stages of the disease the bodies are sparsely present and are exceedingly minute structureless spherules lying in the protoplasm of the nerve-cells. Later the bodies increase in number and size and contain one or more darkly staining granules. Stained by the Nocht-Romanowsky method the bodies are robin-egg blue, the granules darker in color.

Virus.—In rabid animals the virus is found principally in the saliva and in the central nervous system. It is occasionally known to pass into other organs, such as the lacrimal gland and the pancreas. It is never found in the blood or in the liver, spleen, kidney, or the muscle tissues. The contents of the stomach may contain it, owing to the swallowing of the saliva. It affects principally the central nervous system, and is found in the most concentrated form in the medulla oblongata. The virus may be present in the saliva for at least three days before the animal shows any symptoms of madness, and it may be present eight days before any symptoms appear. It may be present in the central nervous system two days before the appearance of any symptoms. The symptoms do not show themselves until the poison or virus has remained in the nervous tissue long enough to produce structural and functional change. After it is introduced into the body it undoubtedly “multiplies itself” during the period of incubation. It is a “solid body,” as it may be removed from the saliva by filtration through porcelain. There is, however, almost undoubtedly a stage of development of the virus when it is small enough to pass through porcelain. An emulsion of brain of an infected dog will give a filtrate infective for rabbits. It is found in human milk, tears, aqueous humor, and cerebrospinal fluid. The virus penetrates to the nervous system by following the nerve-trunks from the site of injury to the spinal cord. This has been proved by comparison of portions of the cord and of the nerves at varying periods after inoculation. The virus is destroyed by drying and by the action of light.

Noguchi has lately demonstrated that the virus of rabies may be cultivated upon anaërobic serum-cultures. It takes the form of minute masses of chromatin surrounded by a clear zone and a membrane, and as very minute granular and somewhat coarser pleomorphic chromatoid bodies. The former multiply by budding and division and suggest

protozoa. Similar pictures may be found by dark-field examination of hydrophobia brains. The bodies are from 1 to 12 μ across.

The loss of virulence by drying is gradual and regular; hence this is taken advantage of for the production of "vaccine." The virus is completely destroyed at a temperature of 50° C. (122° F.) in one hour. It remains uninjured by exposure to extremes of cold—10 or 20 degrees below zero.

The Danger from Bites.—The richer the nerve-supply, the greater the danger, and punctures are more dangerous than lacerated wounds. The wolf, the cat, and the dog, in the order named, are the most dangerous animals.

Period of Incubation.—Man, forty days; cats, fourteen to twenty-eight days; dogs, twenty-one to forty days. Other animals vary from fourteen to fifty-six days.

The Season.—More frequent during the period from April to September than any other part of the year.

Preventive Inoculation.—Pasteur devised a method of treatment which consists essentially in successive inoculations with emulsions of spinal cords of increasing virulence. The virulence of the material used for the first inoculations is decreased by drying the cords for varying periods, and the injections are begun with the older cords and continued with increasingly virulent material.

Pseudohydrophobia or Lyssophobia.—This is simply a condition of fright, and the patients invariably recover.

Pathology.—*Gross Appearances in Organs.*—There is no gross lesion that can be considered specific of the disease. The cadavers are apt to be emaciated and to become putrid rapidly. The blood is usually dark and thick. The brain and the membranes may be congested, and may even show slight hemorrhages. The gastro-intestinal tract and the respiratory tract may be congested and also show slight hemorrhages. Rabid dogs frequently swallow wood, straw, stones, and the like, which are found in the stomach *postmortem*.

Microscopical Appearance.—There is nothing distinctive outside of the nervous system. Changes are found in the ganglia of the cerebro-spinal and sympathetic systems, and are especially marked in the plexiform ganglion of the pneumogastric nerve and in the Gasserian ganglion. Normally, these ganglia are composed of supporting tissue holding in its meshes the nerve-cells. These nerve-cells are surrounded by an endothelial layer and capsule. The rabic virus brings about an abundant multiplication of the cells lining this capsule, leading finally to the destruction of the normal ganglion, and leaving in its place a collection of round cells. All ganglion cells are not markedly changed; some are slightly or not at all changed; others are entirely destroyed. These changes are particularly marked in the dog, less so in man, and still less so in the rabbit. The ganglion of the pneumogastric nerve is the one generally chosen for examination, and it should be removed immediately after death and placed in absolute alcohol or in formalin solution.

RHEUMATISM

Definition.—Acute articular rheumatism is probably an infectious condition; the nature of the infectious agent, however, is uncertain.

Etiology.—The manifestations of rheumatism agree very well with those of infectious diseases, and some of the lesions frequently complicating the disease, such as endocarditis, are invariably infective. The relationship between tonsillitis and rheumatism has been explained by some as that between primary and secondary disorder. It is supposed that the infectious agents effect an entrance into the body through the tonsils, causing primary tonsillitis and secondary general infection, with localization in the joints. In other cases it has been held that the organisms enter through abrasions of the skin or in other ways.

Leyden and others have described a streptococcus, and it has been shown that this organism is capable of producing arthritis, endocarditis, and pericarditis in experimental animals. A considerable number of recent investigators have isolated a micrococcus or streptococcus from cases of rheumatism and have succeeded in producing joint lesions, endocarditis, and pericarditis in animals inoculated with it. Others, however, have produced similar lesions with streptococci from other sources.

The organism now receiving most attention is the *Streptococcus rheumaticus* of Poynton and Paine. This is a hemolytic acidifying diplococcus requiring blood for its best cultivation. It has been found in synovial fluids and tissues, in the blood, and in heart-valve vegetations. It is suggestively like the chorea micrococcus. It produces arthritis and endocarditis in experimental animals.

Achalme described a bacillus which he and others found in a number of cases of acute articular rheumatism. It is a large bacillus resembling that of anthrax; sometimes it is motile; it stains well with anilin dyes and with Gram's stain; may have a capsule, and forms polar spores much larger than the bacillus. This organism is obligate-anaërobic, growing best in liquid media, in which it forms small bubbles of gas. The organism is closely allied to or identical with Welch's *Bacillus aërogenes*. Thioroloix claims to have produced typical symptoms in the rabbit; and the inoculation experiments of others have given suggestive results. This bacillus was obtained from the blood in a number of cases; and from the pericardial fluid and blood in a state of purity in one case. The organisms have been found in sections of the heart muscle and valves.

The fact that one organism or another produces inflammatory lesions in the joints, endocardium, or pericardium of animals when injected intravenously does not prove a specific relation of the organism to rheumatism. Doubtless various organisms are capable of producing such lesions, and it is not improbable that the clinical disease rheumatism may include a variety of infections.

(For the pathological anatomy of rheumatism, see Diseases of the Joints.)

BERIBERI

Definition.—Beriberi, or kakke, is an epidemic or endemic specific polyneuritis, with alterations of sensation and motility, and associated disturbances of digestion. This disease was long regarded as an infection, and in some particulars strongly suggests an infection, but is of uncertain etiology. It occurs in tropical and subtropical countries, and is characterized by muscular weakness, generalized muscle pains, dropsy, and cardiac failure.

Etiology.—Beriberi occurs among young persons and usually affects numbers of people. It is most frequent along ocean coasts and great rivers, and is most prevalent during damp seasons of the year. It does not seem to be contagious. Dietary conditions, such as may arise from defective food on ships and in institutions, appear important in its etiology.

The cause of beriberi is unknown; no virus has been isolated to establish its infective nature, and it is now believed to lie in certain foods, notably, rice and canned meats, of which the former is the more important. In milling and polishing rice, the pericarp, rich in valuable phosphorus, is removed. Much information has been gleaned by the experimental production of a degenerative peripheral neuritis in birds by feeding with such polished rice, and a similar experiment has been made with condemned prisoners. The importance of the unknown substance in the covering of the rice grain is shown by the fact that improvement follows the use of rice-bran in beriberi and experimental polyneuritis. This substance is either necessary to nutrition, or its absence disturbs metabolism in the nervous tissues. Some observers believe toxins are formed by cooking improperly preserved or spoiled rice. Moszkowski produced beriberi in himself by a diet of polished rice. His symptoms indicated no change in the motor nerves, the sensory only being affected, and the reflexes were increased. There was excessive nitrogen excretion, but the phosphorus metabolism seemed normal. The disease may be transmitted to the young through the milk. The form chiefly associated with superficial dropsies is called "kakke," believed by some to be an independent disease. This is denied by others.

The sensory phenomena take the form of areas of reduced tactile sense and are commonly met upon the dorsum of the foot, finger-tips and dorsum of the hand, around the mouth, and upon the abdomen. Edema of the superficial parts may or may not be seen. Then follow palsies of the dorsal muscles of leg and hand, and at times of the cranial nerves supplying face and neck. Death occurs by exhaustion or intercurrent infections. The pathology, except in the nervous system, is in no way specific. There is a slight anemia and leukocytosis. Edema in several isolated areas may be found. Congestions and early inflammations are common. This is particularly true of the gastro-intestinal tract, where the mucosa is cyanotic, but the glands are little if any changed. Parenchymatous degenerations are met. In the peripheral nerves there is degenerative neuritis with increase of nuclei, probably from the sheath of Schwann. The ganglia on the posterior roots and occasionally the roots themselves are degenerated.

PELLAGRA

This is a chronic, relapsing, non-febrile disease characterized by a more or less specific cutaneous eruption and nervous and digestive disturbances. Its etiology is not certainly known, but it has been supposed to be due to the use as food of Indian corn in which a toxin has arisen by infestation with certain *aspergillus* species. This is in accord with its appearance in the spring and summer. Various bacilli and amebæ have been considered causes of pellagra, and lately Sambon asserts that it is transmitted by an insect. Late observations indicate that it may be transmitted to monkeys by Berkefeld filtrates from tissues of human cases. It occurs most commonly in white females between twenty and forty, beginning in May and June. Poor environment and living conditions favor its development.

The cutaneous manifestations take the form of an erythematous dermatitis on exposed parts, which are aggravated by exposure to sunlight. The skin may swell or vesicles may form. The distribution is apt to be symmetrical and the patches limited. Thickening of the superficial layers, with pigmentation and parchment-like appearance, is the common condition in later stages.

The nervous conditions comprise anesthetics, paresthetics, early increase of reflexes, and tremors. Later, evidences of dementia set in.

There is no specific pathology. There are congestion and pigmentation, and sometimes fatty degeneration of parenchymatous organs. Ulcers in the colon may be found. In the nervous system meningitis of a low order, degeneration of a few nerve- and ganglion cells, perivascular infiltration of round cells and degeneration of the posterior and lateral columns have been reported. The cerebrospinal fluid is usually abundant, possibly under pressure, limpid, clear, sterile, and contains some increase in protein and lymphocytes.

There seems to be a lowered and somewhat perverted protein metabolism in pellagra. Judging from the known facts that hyperacidity exists in the stomach, we may assume that digestion is deficient in the intestine.

The microscopical changes in the skin are degeneration in the corium, followed by mild granulation tissue and thickening accompanied by proliferation in the spinous and granular epithelium in which pigment is prominent.

The last two diseases, beriberi and pellagra, seem to be due to the absence from the diet of substances necessary to the construction of the phosphatids of nervous tissue, to which Funk has given the name "vitamins." Their exact nature is not yet clear, but they do not seem to be proteins or carbohydrates.

DENGUE

This is an acute infection common in the tropics, due to a filterable virus, transmitted by the mosquito *Culex fatigans*. The virus is in the blood. There are fever, with an intermission, rheumatoid pains, and varied skin eruptions. One attack gives no immunity.

POLIOMYELITIS

This disease of the central nervous system has assumed a position of great interest during the past decade, for during that time it has been pandemic, at least in Europe and North America. It was formerly known as a sporadic disease of childhood, but its recent manifestations have been those of a transmissible epidemic disease affecting almost any age, though especially frequent in childhood.

The infection begins with a mild febrile attack, to which is shortly added muscular and joint pains, followed by palsy, and later by distinct paralysis. (For the pathology of the disease, see Nervous System.)

Etiology.—The exact nature of the causative agent of this disease is not yet certainly known, but Noguchi has lately been able to cultivate from the central nervous system a tiny, poorly staining, bacterium-like body, with cultures of which he claims to be able to produce the disease in monkeys. Not only has this observer been able to grow these bodies, but he has found them in sections of nervous tissue.

While little is as yet known of this tiny bacterium, much has been learned of the distribution and behavior of the virus. It is to be found in the brain, spinal cord, ganglia, spinal fluid, nasal mucosa, lymphatic organs, and intestinal contents. If emulsions of parts containing the virus be injected into the brain of a monkey the animal will develop symptoms, signs, and the pathology of poliomyelitis. If, instead of the emulsion, a filtrate of it, through a Berkefeld filter, be used, infection will also result; the virus is, therefore, filterable. Heating to 50° C. (122° F.) one-half hour destroys the virus, but it will withstand drying, 50 per cent. glycerin, and tissue autolysis. The virus is said to be constantly in the nasal secretions of infected persons, sometimes in those of attendants, and also in surroundings, notably in dust.

Transmission.—Two theories are proposed for the transmission of poliomyelitis: first, that it is spread by insects; and, second, that contact, direct or indirect, is responsible.

The insect transmission theory is based upon the appearance of the disease usually in summer, and upon the discovery by Rosenau that it was possible to transmit the disease from monkey to monkey by the bite of the stable fly (*Stomoxys calcitrans*).

The contact infection theory is based upon the fact that the virus is present upon and in the nasal mucosa of patients and healthy attendants. The latter are suspected of being carriers. Much more important than these, however, are the so-called "abortive" cases of poliomyelitis. These are instances in which only a mild febrile affection occurs, but which do not go on to palsies, or, at most, show only transient weakness; therefore, so atypical that they escape recognition, and, going abroad, actively disseminate the virus.

The nose as a portal of entry gains somewhat in probability when one considers the short distance the virus has to travel to reach the central nervous system by passing along the olfactory tract.

Immunity.—One attack of poliomyelitis, either natural or experi-

mental, gives immunity, but this immunized power cannot be transferred to another individual. As yet no therapeutically valuable anti-serum has been found. The serum of an immune person or animal does, however, possess the power to neutralize the virus. If such a serum and a known virus be mixed, incubated, and injected into a monkey, no paralysis will occur, while a control animal injected with the same virus not exposed to the immune serum will develop poliomyelitis. This test has made it possible to detect abortive cases, because no uninfected person gives serum with this property.

FOOT-AND-MOUTH DISEASE

This infection of cattle may be transmitted to human beings who use milk from affected cows, or directly from infected animals. There is a vesicular eruption in the mouth and on the feet and hands comparable to the lesions in cows. The virus is in the vesicular fluid; it has not been cultivated, but is filterable. One attack probably gives no immunity; the blood-serum has therapeutic and preventive properties.

TRACHOMA

This is a transmissible disease of the conjunctiva characterized by tiny granulations on the palpebral surfaces, said by some to be due to an invisible filterable virus; by others it is believed to be caused by an influenza-like bacterium. Some observers have found an intracellular body which they believe to be the cause. This has been placed among Prowaczek's Chlamydozoa. (See chapter on Eye.)

ROCKY MOUNTAIN FEVER

This is an acute transmissible disease characterized by evidences of general infection, severe pains, and a macular or erythematous eruption. It is transmitted by the tick *Dermacentor occidentalis*. It is practically confined to the Rocky Mountain States and is most frequent and severe in Montana. It is a disease of adult life, occurring chiefly among those who work abroad, and is prevalent in summer. The tick obtains the virus by blood-sucking, and transmits it to another person by biting. The female tick transmits it to the eggs and young. The virus is in the blood of the patient and is destroyed if this be heated to 50° C. (122° F.) or is dried; it will not pass a Berkefeld filter. The disease may be transmitted by the introduction of infected blood into a guinea-pig, rabbit, or horse, and the clinical course in these animals is closely comparable to that seen in man. The serum of experimentally infected animals has an immunizing value for other animals, but it possesses little if any therapeutic power. It has been claimed that there is in the infected blood and ticks a minute diplococcoid body resembling an organism of the hemorrhagic septicemia group. No bacteriological cultivation has been successful, so that the cause of the disease is not known. One attack, in the laboratory animals at least, confers immunity.

THE CHLAMYDOZOA

This is a name given by v. Prowaczek to certain intracellular bodies whose zoölogical position is not clear, but which have some characters suggestive of the protozoa. They undergo a change in appearance which has been interpreted by some observers as a metamorphosis. No exact life cycle has been accepted by all authorities as certainly pointing to protozoal nature. The group includes the Negri bodies of rabies, the cytoxyctes of vaccinia and variola, the cyclasterion of scarlet fever, the trachoma bodies, etc. Prowaczek and his followers interpret these chlamydozoa as the result of cellular infestation by ultramicroscopical bodies, in response to which the nucleus or nucleolus extrudes into the cytoplasm some of its material. The intracellular body seems at first to be either a clear space or a minute dot until it is surrounded by the chromatin material as above derived. The chlamydozoön then assumes the form of an irregular mass of chromatin with one or more clear spaces. It appears in any imaginable form, giving the impression of metamorphosis. Cytoplasm seems to form, but if this be *de novo* or only a part of altered cell protoplasm is not known. The virus causing these protozoön-like changes within the cell is filterable, associated with colloids, and has a predilection for epiblastic tissues. No chlamydozoön is known apart from the cell manifestation, and none has been cultivated.

CHAPTER X

ANIMAL PARASITES AND DISEASES CAUSED BY THEM

PROTOZOA

Classification.¹—**CLASS I.** *Rhizopoda* (Sarcodina), forms resembling the ameba, and characterized especially by the presence of pseudopods.

CLASS II. *Flagellata* (Mastigophora), protozoa characterized by the presence of one or more long lash-like flagella, used for progression or acquirement of food.

CLASS III. *Sporozoa*, forms living as parasites in the tissues of other animals, receiving their food only by osmosis. Reproduction by means of encysted spores.

CLASS IV. *Infusoria* (Ciliata), cell-body of fixed shape with cilia; living free in water or as parasites.

CLASS V. *Suctoria*, cell-body provided with suckorial tubes. Usually ectoparasites in water animals and plants.

The protozoa differ from the bacteria in producing a progressive disease without evidences of immunity. Trypanosome infection shows the presence of some immune bodies in the blood, but any increase of antiprotozoal power of the serum does not seem to limit the course of disease, nor can the serum be used to immunize another person.

Some of the protozoa produce a toxin, but most of them exert their noxious power by mechanical injury or obstruction, acting with the products of tissue destruction or with bacteria. Protozoa do not as a class have a pronounced chemotactic power for leukocytes. They produce proteolytic enzymes and their activity is followed by an increase of acid in their vicinity.

Most protozoa have tissues of predilection, such as malaria plasmodia, the blood; amebæ, the colon and liver; sarcosporidia, the muscles.

RHIZOPODA

ENTAMOEBA HISTOLYTICA

Description.—This organism is an ameboid body from 20 to 30 μ in diameter, consisting of a clear protoplasmic refractive outer portion and a finely or coarsely granular protoplasm within (Fig. 128). It frequently shows vacuoles and sometimes a vesicular nucleus. It presents active ameboid movements when studied on a warm stage of the microscope; and frequently contains foreign bodies, such as bacteria, pigment-particles, and portions of blood-corpuscles or other cells.

In the movements of the organism pseudopodia are projected from some part of the periphery. These at first draw upon the clear peripheral zone, but after their formation the granulooplasm flows into the projected pseudopods. When in unfavorable surroundings the organ-

¹ Braun, *Die tierischen Parasiten des Menschen*, 1903.

ism undergoes a form of change called the *encysted state*. In this the body becomes spherical, and the wall is eventually stiff and firm, and usually presents a double contour. The division into a clear and a granular protoplasm is lost, the organism being uniformly granular.



Fig. 128.—*Entamoeba histolytica*. Living organisms. Note absence of nucleus. All three of the parasites contain red blood-corpuscles; $\times 750$ (Bulletin No. 1, Medical Department U. S. Army, 1913).

Schaudinn differentiates two forms of the dysentery amebæ, calling them *Entamæba histolytica* (Fig. 128) and *Entamæba tetragena* (Fig.

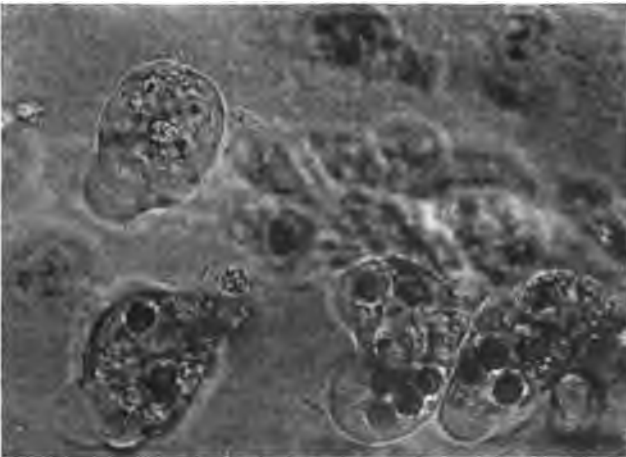


Fig. 129.—*Entamoeba tetragena*. Living specimens. Note nucleus in upper entameba. The three lower entamebæ contain red blood-corpuscles; $\times 750$ (Bulletin No. 1, Medical Department U. S. Army, 1913).

129). Craig and others now consider them to be different stages of development of the same species, but this opinion is not held by all parasitologists.

Distribution and Pathogenesis.—The organism in question has been found abundantly in the stools of patients suffering from dysentery. It is readily detected in the necrotic particles or the mucus of the stools, and has also been found in the tissues of the bowel wall adjacent to the dysenteric ulcers and in the liver abscesses secondary to dysentery.

Liver abscess is a frequent complication or sequel of amebic dysentery. The protozoa reach the liver through the blood-stream, probably by penetrating radicles of the mesenteric vein, and are found in the wall of the abscesses. Whether they alone can produce pus is not known. There may be abscesses elsewhere.

Musgrave and Clegg have cultivated amebæ with cultures of bacteria, and should a colony grow free of bacteria it may be kept alive for a short time on an agar media to which extracts of tissue have been added. The injection of mucus containing the amebæ into the rectum of cats and other animals has occasionally produced typical dysentery, but this does not prove the pathogenicity of the amebæ. Lesions closely similar to the natural disease have been produced in monkeys, and a human case with very suggestive clinical course was caused by swallowing capsules containing amebæ. The *Entamæba histolytica* produces a moderately strong poison which causes cellular necrosis, but not much acute inflammation.

ENTAMÆBA COLI

This smaller ameba (10 to 20 μ in diameter), also differing from the *Entamæba histolytica* in having a less greenish color, less distinct ectoplasm and endoplasm, less distinct pseudopodia, in the usual absence of vacuoles, the almost invariable presence of a nucleus and well-defined nuclear membrane, and in rarely ingesting red corpuscles, has been found in the feces of from 50 to 70 per cent. of healthy persons in various localities. Possibly under certain conditions the ameba may become pathogenic; usually it has been found in persons entirely well.

OTHER AMEBÆ

Several other amebæ of lesser importance have been discovered. Among these are the *Entamæba urinalis*, found in the urine in cases of cystitis, and several forms met with in the mouth, especially about the teeth. *Entamæba buccalis* has lately been held responsible for pyorrhœa alveolaris. An ameboid organism of uncertain pathogenic significance has been discovered in the abdominal fluid of cases of ascites. It has been named *Leydenia gemmipara*. It has a pulsating vacuole and nucleus and multiplies by budding or division.

MASTIGOPHORA (*Flagellata*)

CERCOMONAS HOMINIS

This organism is a pear-shaped body with a sharp anterior extremity provided with a delicate short cilium. The broader posterior end is

provided with a long, tail-like flagellum. A large and a small variety have been described (Fig. 130). The former is the variety usually found and is from 10 to 12 μ in length. A minute oval aperture has been found at the anterior extremity.

Significance.—The organism has been discovered in great numbers in various diarrheal conditions, especially in cholera. It has, however,



Fig. 130.—*Cercomonas hominis*: A, large; B, small, variety (Davaine).

been found in the stools of from 10 to 25 per cent. of healthy persons in tropical countries and is not known to have definite pathogenic powers. It is not improbable that the organism is, in reality, a form of *trichomonas*.

Other closely allied cercomonads have been found in the urine (*Bodo urinarius*, *Cercomonas urinarius*).

CERCOMONAS COLI HOMINIS

A single observation of this organism was made by May. The body of the parasite was not quite the size of a red corpuscle; rather granular and glistening and slightly greenish. It was spindle shaped, the anterior end more blunt than the posterior. Four cilia were found attached to this end, and upon one side of the organism was seen an undulating membrane. In the same case smaller bodies, less developed and probably younger parasites, were discovered. The patient suffered from carcinoma of the stomach and chronic diarrhea.

TRICHOMONAS INTESTINALIS

This organism is pear shaped; from 10 to 15 μ in length and 7 μ in breadth (Fig. 131). The anterior end is blunt; the posterior end is



Fig. 131.—*Trichomonas intestinalis* (Zenker).

prolonged into a sharp, tail-like projection. The body is granular and contains one or two bodies resembling vacuoles. Near the anterior end at one side may be seen a row of ten or twelve cilia, which give the organism active motility. It has also ameboid movements.

Significance.—This organism has been found in cases of diarrhea, but its significance is doubtful.

TRICHOMONAS VAGINALIS

This form is rather smaller than the last, with an attenuated caudal end and a more blunt anterior portion, provided with three or four flagella; there is a lateral undulating membrane with six or seven short cilia.

Significance.—The organism has been found in cases of vaginitis due to various causes, but also in the vagina in the absence of evident disease.

It has been claimed by some writers that the four forms of flagellates just described are, in reality, but variants of a single species or inaccurately described members of the same variety. They accompany some forms of amebæ. Their most important pathological seat is the bladder, where they can set up an irritation.

OTHER FORMS OF TRICHOMONAS

Sternberg has found several forms in the mouth, and especially about the teeth. These have been termed *Trichomonas flagellata*, *T. caudata*, and *T. elongata*. A trichomonas closely related to *Trichomonas vaginalis* has been found in gangrene of the lung and in putrid bronchitis.

LAMBLIA INTESTINALIS

This organism in its active state is irregularly pear shaped, and presents at its broad end a cup-shaped depression situated obliquely at

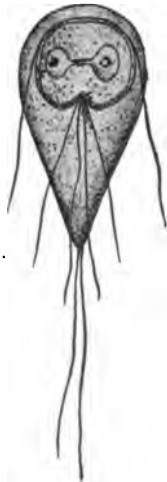


Fig. 132.



Fig. 133.

Figs. 132 and 133.—*Lamblia intestinalis* from the intestines of a mouse (Grassi and Schewiakoff).

one side (Figs. 132 and 133). On the anterior edge of the depression are attached two long cilia, and at one point of the posterior lip are two pairs

of cilia. In the base of the depression are seen two vesicular structures (nuclei) united by a band. The protoplasm is finely granular and is surrounded by a delicate capsule. When free the organism is capable of rather rapid motion, but in the intestine it is attached to the epithelial cells by its cup-shaped depression. The organism exists in this form in the duodenum and jejunum. In the colon or other unfavorable situations it forms oval encysted bodies showing the nuclei and cilia within.

Significance.— *Lamblia* is a frequent parasite of the mouse, but has been found in the intestines of other animals, and occasionally in man. It has been found especially in chronic diarrheal conditions, and at times appears in the stools in immense numbers. No definite lesions have been found, and the pathogenicity of the germ is uncertain.

TRYPANOSOMA

Several varieties of trypanosomes have been recognized in animals, notably in horses and cattle. Among these, *Trypanosoma evansi* (Steel) has been found in the disease "surra" in horses and mules in India and Burmah; the *T. brucei* (Plimmer and Bradford) has been found in "nagana," a disease of horses and cattle in Central Africa; a form probably identical with *T. brucei* has been found in "mal de Caderas," a disease similar to surra and nagana in Central South Africa and Brazil; *T. equiperdum* (Doflein) or *T. rougeti* (Laveran) in the disease of horses known as "dourine" in Algeria and other countries. A comparatively harmless variety (*T. lewisi*, Kent) occurs in a large proportion of wild rats. It has been the form on which many of the studies of trypanosomes have been made. A few other forms have been recognized.

The trypanosome was discovered in the blood of a human patient by Dutton. The earlier reported cases of Nepvieu are open to some doubt. Dutton's patient, an Englishman, had been along the Gambia River, and his symptoms were much the same as those met with in animals from the same parasitic invasion. Great wasting and weakness, especially in the legs; irregular relapsing fever; edema, especially about the eyes; injection of the skin and conjunctivæ; enlargement and tenderness of the spleen, and frequent pulse and respirations, were the principal symptoms. Castellani announced in 1902 his discovery that the sleeping fever of the African negro is caused by a variety of trypanosome.

The name *Trypanosoma gambiense* (Dutton) has been proposed for the parasite of man (Fig. 134).

The trypanosome is a minute, worm-like body, difficult to see in the fresh blood with a magnification of 300 diameters. One end of the parasite is drawn out into a flagellum; the other end is bluntly conical. An undulating membrane is attached along the body, which is short, thick, and granular. Near the posterior end is found a refractile spot (vacuole). The parasite moves forward or backward by means of the flagellum, but usually toward the direction of the flagellated end. Reproduction occurs by longitudinal fission, and, in addition, it is

thought, can occur by sexual reproduction. The organism readily dies in fresh preparations. In the stained preparation it was found 18 to 25 μ in length and from 2 to 2.8 μ in width.

Novy and McNeal succeeded in cultivating trypanosomes in artificial media composed of 1 part of nutrient agar and 2 parts of fresh defibrinated or laked rabbit or rat blood. The organisms retain their virulence in cultures for long periods of time.

The trypanosome of man has been found pathogenic for certain monkeys and for dogs, cats, and rats.

Transmission of the Disease.—The transmission of the parasite is effected by various blood-sucking flies. The *Trypanosoma gambiense* is conveyed by the *Glossina palpalis*; *T. brucei*, mainly by the tsetse fly, *G. morsitans*; *T. lewisi*, by fleas. The fly conveying the human parasite acts as a host, for it becomes infective three days after biting, and remains so four weeks, thus indicating that some form of metamorphosis takes place.



Fig. 134.—*Trypanosoma gambiense*: (1) From the blood; (2) from serosanguinolent fluid; (3) form showing rounded posterior extremity and granular protoplasm; (4) dividing form; \times about 2000 (Laveran and Mesnil).

The organism may exist in the blood of man for a long time without causing symptoms. Later it enters the cerebrospinal fluid and then causes the characteristic manifestations. As a rule, there is first irregular fever, later pains and swelling of the extremities, and finally coma.

The lesions discovered at autopsy consist of cerebrospinal meningeal congestion with increased fluid, and enlargement of the spleen and liver. The cerebrospinal fluid is in excess and cloudy, but not purulent. The arachnoid may be lifted from the convolutions and the pia has been found abnormally tight. The lymph-nodes are almost universally enlarged and the spleen frequently shows a myeloid transformation.

Immunization of animals has been accomplished by repeated inoculations and immune sera of decided potency have been produced.

Human trypanosomiasis is transmissible to monkeys.

Leishmaniasis.—This term may be given to a group of three diseases prevalent in Africa and Southern Asia, known as “kala-azar” or “dumdum fever,” “infantile kala-azar,” and “oriental sore” or “Aleppo

button." The causative organism is a near relative of the trypanosomes, among the Flagellata. The symptoms of the first two are moderate anemia and fever, associated with splenomegaly. The spleen shows little microscopical change aside from hyperplasia. The prognosis is grave. Oriental sore is characterized by the appearance on skin surfaces of spreading suppurating and ulcerating granulomata. These lesions tend to heal and leave disfiguring scars.

The causative organism is known as *Leishmania donovani*, after the men who discovered and described it. It varies but slightly in the three clinical forms above, only differing in size and appearance upon cultivation. It may be grown upon the medium described for trypanosomes. In the body the parasite exists as an intracellular round or oval (2.5 by 3.5 μ) mass containing two more deeply staining large granules. The larger, or nucleus, lies excentrically, parallel to the



Fig. 135.—*Leishmania donovani*. Flagellated forms from a culture. Wright's stain; $\times 1800$ (Bulletin No. 1, Office of the Surgeon General, January, 1913).

long axis of the parasite. The smaller granule is probably the blepharoblast. Vacuoles may be present. The parasites stain palely, while the granules are dark. They lie within lymphocytes and endothelial cells. They do not appear in any numbers in the circulating blood, but may be found in lymph-tissue and marrow (Fig. 135).

The manner of transmission is not known, but insects and bedbugs are suspected.

Histoplasmosis is a condition characterized by anemia, prostration, splenomegaly, fever, and emaciation, caused by the *Histoplasma capsulatum* (Darling), a flagellate related to the trypanosomes. The organs may occasion spreading granulomata and the intestines show ulceration. The organism is intracellular, has an irregular oval nucleus, vacuoles, and a wide capsule. The organism has not been cultivated. The disease was found in the Panama Canal Zone.

HEMOSPORIDIA

THE PARASITES OF MALARIA

The organisms which are now recognized as the cause of malaria belong to the protozoa. Most authors regard them as Sporozoa, suborder Hemosporidia. They are found in the blood and the vascular channels of the various organs, deriving their nourishment, for the most part, directly from the blood-corpuscles.

Malaria has been regarded as a water-borne and as an air-borne disease, but no proofs have been obtained for either view. Direct contagion does not occur, but it has been shown that the blood is infectious when introduced into the circulation of a healthy person. The drinking of the blood does not give rise to the disease. Certain external condi-

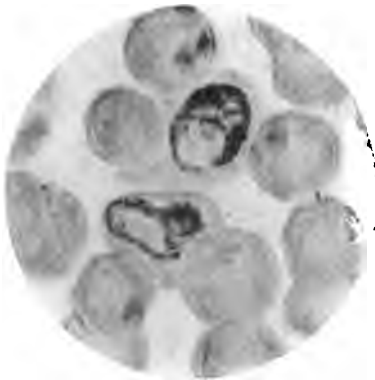


Fig. 136.—*Plasmodium vivax*. Half-grown parasite. Wright's stain; $\times 1500$ (Craig, Bulletin No. 6, War Department).



Fig. 136a.—*Plasmodium malariae*. Half-grown parasite, the so-called band form. Wright's stain; $\times 1800$ (Craig, Bulletin No. 6, War Department).

tions are favorable or necessary to the development of the disease. These external conditions are moist, marshy soil, atmospheric humidity, and high temperature. The disease occurs in the lowlands or bottomlands, and very rarely in high and dry ground. Extensive excavations and the like may cause the appearance of the disease or increase it, and, on the other hand, suitable drainage may cause its diminution or disappearance. The relation of all these conditions to malaria is explained by the demonstration of the part played by mosquitoes in the transmission of the contagion.

Three distinct species have been identified: the organism of tertian fever (*Plasmodium vivax*, Figs. 136–138), that of quartan fever (*P. malariae*), and that of estivo-autumnal fever (*P. falciparum*). Each of these has a double life cycle, one within the human host, the other in the body of the mosquito. In the human circulation, spleen, or elsewhere asexual reproduction (*schizogony*) of the parasite occurs until it

has exhausted its reproductive power or antagonistic bodies have destroyed it; while in the mosquito sexual reproduction (*sporogony*) occurs by conjugation.

Plasmodium Vivax.—The cycle of development in the blood of man begins with a small hyaline spherule (*schizont*) about $2\ \mu$ in diameter which is attached to and later within a red corpuscle. Soon pigment particles appear within the parasite, being derived from altered hemoglobin. The pigment particles are more or less actively motile, due to currents in the protoplasm. Later the body increases in size and the corpuscle in which it is contained swells and becomes paler. Finally, the sphere increases to perhaps twice the size of a normal corpuscle. In all stages ameboid changes in the shape of the organism may be observed, but become less and less marked as the plasmodium enlarges. In the spleen, and to a less extent in the circulating blood, division of the



Fig. 137.—*Plasmodium vivax*. Fully developed macrogametocyte. Wright's stain; $\times 1800$ (Bulletin No. 1, Medical Department U. S. Army, 1913.)



Fig. 138.—*Plasmodium vivax*. Fully developed microgametocyte. Wright's stain; $\times 1800$ (Bulletin No. 1, Medical Department U. S. Army, 1913.)

parasite may be observed about the time of the expected paroxysm of the disease. The pigment collects in the center, the organism forms a rosette and then divides into fifteen or twenty rounded segments or *merozoites*. These escape from the destroyed red corpuscle and are then ready to attack a new corpuscle and begin the same cycle.

In the earlier stages the hyaline body appears as a light area on an otherwise normal red corpuscle; somewhat later its rounded shape suggests a ring and the term "ring-bodies" is given. This is conspicuous in preparations stained with a chromatin stain such as in the Nocht-Romanowsky method. The body of the parasite is blue and at one point in the periphery may be seen red chromatin matter, thus suggesting a signet ring. Before segmentation the chromatin collects in the center and eventually divides, a portion being found in each of the merozoites. The cycle of development of this form occupies about forty-eight hours.

Plasmodium Malariae.—The organism of quartan fever differs from the tertian in that it is less pigmented and the pigment is usually coarser, more characteristically arranged at the periphery of the parasite, and usually motionless. The segmentation is more regular, forming a wheel-like figure with nine to twelve segments which form the sporules or merozoites. The segmentation occurs only in the circulating blood and the cycle occupies seventy-two hours. The corpuscle containing the organism does not enlarge nor grow pale as in the case of the tertian form, but instead presents a greenish appearance.

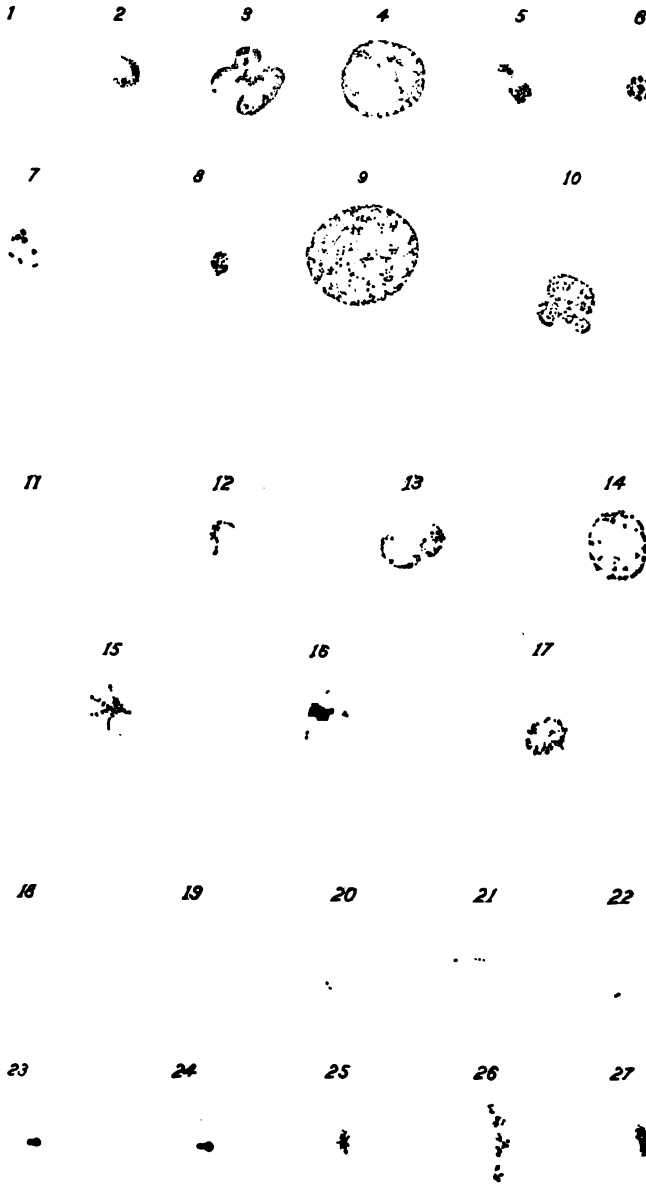
Plasmodium Falciparum.—The organism of estivo-autumnal fever is believed by Italian and tropical investigators to occur in two forms: a tertian and quotidian, which have certain distinguishing features. The organism is characterized by its tendency to develop marked signet-ring forms, by its relatively small size, and by its fine granulation and highly refractive protoplasm. Segmentation occurs in forty-eight hours and takes place mainly in the spleen, bone-marrow, liver, and capillaries of the brain. The segments are from seven to ten in number.

Sporogony.—A certain number of the plasmodia of any one of the three varieties, when of mature size, instead of undergoing segmentation become differentiated as male and female forms or *gametocytes*. In the tertian and quartan varieties the male form, or *microgametocyte*, is a rounded body with centrally placed nucleus, having an abundance of chromatin and a considerable amount of actively motile and diffused pigment matter (Fig. 138). The *macrogametocyte*, or female form, has an excentrically placed nucleus with less chromatin and coarser pigment arranged in clumps about the periphery of the organism (Fig. 137). In the case of the estivo-autumnal parasite the gametocytes first appear as oval bodies within the red corpuscles, but soon they assume the well-known form of *crescents*, which even when quite mature may present on the concave border remains of the red cell in which they developed. The crescent contains rod-shaped pigment in a cluster either at its center or one pole, and a male and female form can be distinguished. These sexual forms (gametocytes) of malarial plasmodia are less abundant in the earlier stages of infection than later when schizogony or asexual division becomes less active.

When blood is drawn and kept for a time under a cover-glass further changes take place in the gametocytes, which are similar to those which occur in the body of the mosquito. The microgametocyte presents active movements of its pigment and finally a protrusion of several flagella which extend to two or three times the diameter of the cell. These flagella, or *microgametes*, the male element concerned in the process of fertilization, become detached from the cell and penetrate the female organism, macrogametocyte, after the latter has undergone a preparatory change (certain nuclear extrusions) and has thus been converted into a *macrogamete*. Further stages in the sexual cycle of reproduction occur only in the body of the mosquito.

Parthenogenesis.—It has been claimed by Schaudinn, but denied by others, that parthenogenesis of the macrogametocyte may restore to the

PLATE 2



Various forms of malarial parasites (Thayer and Hewetson): Figs. 1 to 10 inclusive, tertian organisms; Figs. 11 to 17 inclusive, quartan organisms; Figs. 18 to 27 inclusive, estivo-autumnal organisms.

FIG. 1.—Young hyaline form; 2, hyaline form with beginning pigmentation; 3, pigmented form; 4, full-grown pigmented form; 5, 6, 7, 8, segmenting forms; 9, extracellular pigmented form; 10, flagellate form.

FIG. 11.—Young hyaline form; 12, 13, pigmented forms; 14, fully developed pigmented form; 15, 16, segmenting forms; 17, flagellate form.

FIGS. 18, 19, 20.—Ring-like and cross-like hyaline forms; 21, 22, pigmented forms; 23, 24, segmenting forms; 25, 26, 27, crescents.

blood a new generation of merozoites when schizogony is becoming feeble. According to this view, the gametocytes represent resistive forms which are able to withstand unfavorable conditions developed in the course of an infection (antibody formation?). The female, or macrogametocyte, is particularly resistive, may remain in the blood after other forms have disappeared, and may then by a process of parthenogenetic segmentation produce a new generation of merozoites. This theory would explain certain cases of late reappearance of infection after apparent recovery.

Bass has lately succeeded in cultivating the asexual cycles in the species of vivax and falciparum by using equal parts of 0.5 per cent. glucose bouillon and blood, or Locke's fluid minus calcium chlorid plus ascitic fluid. The blood is defibrinated in flat-bottom tubes of such size that the clear fluid layer above the cells is at least $\frac{1}{4}$ inch in height. The parasites grow in the upper layer of red cells and can be transferred by a pipet to fresh tubes of uninjured cells for a secondary growth. Leukocytes and serum are prejudicial to the growth of the plasmodium; the former by phagocytosis, the latter by lytic effects.

The Relations of the Mosquito to Malaria.—It has been positively demonstrated that when certain mosquitoes (of the genus *Anopheles*) are allowed to feed upon malarial patients and later upon normal individuals, the latter acquire the disease. Also, it has been shown that susceptible persons may live in the most malarious districts without acquiring the disease, provided they are carefully screened from mosquitoes. Some of the earlier investigations in this direction failed because specimens of *Culex* and other genera (not *Anopheles*) were used. The *Anopheles claviger*, *maculipennis*, or *quadrimaculata* and others of this genus alone seem capable of conveying the disease. When the mosquito takes the blood of the malarial patient into its stomach (midintestine), flagellate forms (microgametocytes) are developed, and the flagella (microgametes), each containing some part of the nuclear substance of the parent cell, are discharged, and, moving toward other of the parasites which do not form flagella (macrogametes), fertilize these by penetration. The fertilized parasites then invade the intestinal walls, entering between the epithelia, and lodge in the surrounding tissues, where they segment and develop a distinct capsule. The cystic structures so formed (oöcysts) contain numerous minute rods or sporozoites that have resulted from the segmentation of the parasite. The oöcysts project into the coelom cavity of the mosquito and eventually rupture into this, whence the sporozoites, discharged into it, are carried to different parts of the body and eventually to the salivary glands, from which they are introduced into any person subsequently stung by the insect. In this manner the extracorporeal cycle of development of the organism is completed and the perpetuation of the disease provided for.

The recognition of the relation of the mosquito to malaria explains certain hitherto obscure facts regarding the conditions that favor the development of the disease. This knowledge has also led to the introduction of sanitary measures that have proved extremely useful.

Pathological Anatomy.—The most important fact in malarial infection is the destruction that it occasions in the blood. Rapid anemia with liberation of the hemoglobin (hemoglobinemia) and the appearance of granular pigment in the blood are among the results. The pigment accumulates in the spleen, liver, bone-marrow, and in other situations. Extreme disorganization of the blood may occasion hemoglobinuria and widespread pigmentation. Congestive enlargement of the spleen, and, after long-continued attacks, cirrhotic changes in that organ, may be observed. Thrombi of the capillaries and arterioles are not rare, and to these, in part at least, are due the focal necroses observed in the liver and elsewhere. The anemia is usually ascribed to the continued attacks of the parasites upon successive numbers of erythrocytes; some late observations lay the hemolysis to the circulation of free hematin, which substance, if injected into rabbits, produces a blood-picture like that seen in human malaria.

Pathological Physiology.—The curiously paroxysmal seizures of malaria are probably the result of the liberation of toxic substances at the time of segmentation of the hematozoön. The periodicity depends upon the cycle of development of the organism. A single group of tertian organisms causes a tertian fever (a paroxysm every other day). Infection with two groups of tertian organisms, maturing on alternate days, produces a quotidian fever (a paroxysm every day). One group of quartan organisms causes quartan fever (a paroxysm every third day); three groups (maturing on successive days) cause quotidian fever. The febrile course in estivo-autumnal infection is more irregular, and this is explained by the discovery of organisms of various ages in the blood. Thus there results a constant succession of maturations and segmentations with less distinct periodicity, because the intervals which occur in tertian and quartan infection are wanting.

Texas Fever of Cattle.—This disease is of interest in connection with malaria because of the relationship of the parasitic cause. The organism is a small, actively ameboid body which occupies the red blood-corpuscles. Frequently it occurs in pairs in the corpuscles, and the name *Piroplasma bigeminum* was given to it on this account. Texas fever is characterized by acute fever and frequently by hemoglobinuria. The spleen is enlarged and hemorrhages are observed in various organs. When the blood of a diseased animal is injected into a healthy one, the latter acquires the disease. Transmission has been traced to the cattle tick (*Ixodes bovis*). The mother tick, after its detachment from the infected animal on which it has fed, transmits the infectious agent to its larvæ through the ova. The young ticks then convey the infection to healthy cattle.

Sporozoa in Birds and Cold-blooded Animals.—Many blood parasites have been studied in birds, reptiles, and other cold-blooded animals. In birds two species, *Hæmoproteus danalewskyi* and *Halteridium danalewskyi*, have been closely studied, thus throwing much light on the life history of the malarial organisms.

COCCIDIA

COCCIDIUM CUNICULI

Description.—The coccidia are small bodies from 30 to 40 μ in length and from 15 to 20 μ in width, having a delicate outer coating, and within this a tough, double-contoured capsule. The body is filled with granular material, which is not rarely aggregated in the center. Outside the body sporulation takes place. The granular protoplasm divides into four rounded capsulated spores, each containing a granular

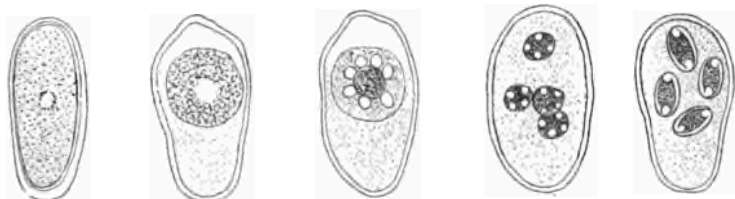


Fig. 139.—*Coccidium oviforme*, showing method of reproduction.

resting body lying in the concavity between two sickle-shaped daughter-spores. Sometimes endogenous sporulation is said to occur, the parasite simply breaking up into a large number of sickle-shaped bodies. The term *psorospermia* is applied to the rounded spores found in the coccidium (Fig. 139).

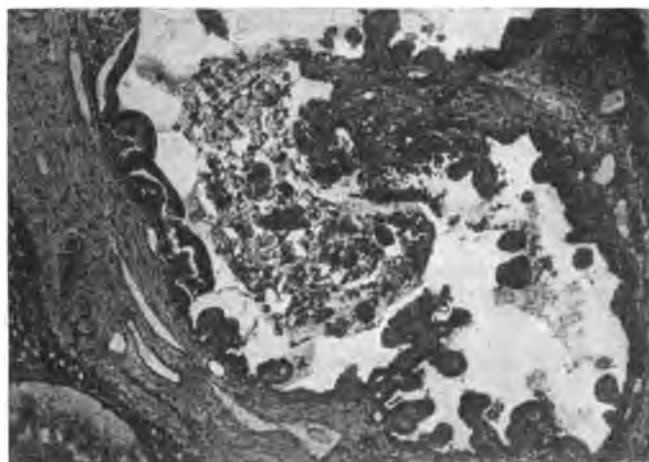


Fig. 140.—Coccidia in the wall of the bile-duct. The cut shows in the center active proliferation of the wall of the duct, with numerous ovoid coccidia massed in the tissue.

The coccidium can also pass through a sexual reproduction (sporogony) with a cycle comparable to that of malarial parasites in the development of young and adult male and female forms.

Occurrence and Pathogenesis.—The coccidium is a frequent parasite of rabbits and certain other animals. It leads to the formation of

yellowish nodules in the liver. It is an intracellular parasite, first invading the cells of the biliary passages and afterward the surrounding hepatic cells as well (Fig. 140). Less frequently it occurs in the intestinal tract, giving rise to nodular thickenings or ulcerations.

The parasite escapes from the body in the stools and then undergoes sporulation. Other animals are probably infected by ingestion of the spores or sporulating coccidia. Occasionally the disease decimates rabbits or guinea-pigs kept in confinement. The animals become languid, lose their appetite, emaciate, and have fever. Later they suffer from convulsions, stupor or coma, and die in this condition.

A few cases of coccidial disease of the liver have been observed in man. The lesions present themselves as cystic nodules springing from the bile-ducts, or less commonly as a diffuse involvement of the liver with cirrhosis and causing jaundice. Coccidial lesions of the intestines have also been discovered in man, and less commonly invasion of the heart, of the kidneys, and other parts.

The close association of the organism with the lesions, and the number of organisms discovered in the tissues, justify the belief that it is the specific cause of the lesions.

The coccidium of the intestinal tract is generally smaller and the sporulation more rapid than that of the hepatic form. It was, therefore, supposed by Leuckart to be a special variety, and has been called *Coccidium perforans* or *C. hominis*. More recently this has been regarded as identical with the ordinary form.

Coccidium Bigeminum (Stiles).—This variety has been found in dogs, cats, pole-cats, and man. The cyst divides into two parts and then forms four spores.

Eimeria Hominis.—*Eimeria* is characterized by the formation in each adult parasite of a single spore containing an indefinite number of sporozoites. The *Eimeria hominis* was discovered in the purulent exudate of a case of pleurisy. The spores were of large size and contained from ten to twenty sporozoites, accompanied by a protoplasmic remnant. The exact origin of the organisms in this case was not determined. Somewhat similar organisms were found by Virchow in a tumor of the liver, and by Severi in the lung.

SARCOSPORIDIA

The sarcosporidia, also called "Rainey's" and "Miescher's tubes," are met with in a number of mammals. The organism is composed of a protoplasmic mass covered with a capsule, and forming at the stage of maturity a large number of sickle-shaped or falciform sporozoites. The organisms usually occur in muscles, either within or between the muscle bundles, and are, therefore, elongated or tubular in shape. In connective tissues the organism may be rounded and sometimes grows to the size of a small cherry. Several varieties have been described, and a few observations have been made in man.

INFUSORIA

BALANTIDIUM COLI

Balantidium or *Paramecium coli* is a rounded body from 0.07 to 0.1 mm. in length and slightly less in breadth (Fig. 141). It is surrounded by a coat of cilia closely set. There is an oral aperture at one end and an anal opening at the other. The substance of the parasite is granular, and contains a bean-shaped nucleus, within which is a round nucleolus and two contractile vacuoles, besides various foreign matters. The parasite possesses ameboid motion. Encysted forms with a thickened capsule have been described.

Significance.—The hog is the natural host of this parasite. Man is probably infected through drinking-water or contaminated food-stuffs. It is found particularly in the northern countries of Europe, and occurs in cases of diarrhea, principally involving the large intestine. The parasite penetrates between the epithelial cells by its ameboid motion. Chronic catarrhal inflammation and dysenteric lesions have been described. The lesions are chiefly purulent, necrotic, and ulcerative in the colon. The parasite may be found mixed with the degenerative mass. Occasionally liver abscess is seen and a penetration to the blood-vessels has been observed. It is possible for it to penetrate the lymph-nodes of the intestinal wall or as far as the mesenteric glands. The organism is probably irritating, but whether pathogenic or not is unknown. Epidemics have been observed in monkeys, the manifestation being prolonged diarrhea.



Fig. 141.—*Balantidium coli* (Malmsten).

Balantidium Minutum.—This species resembles the *Balantidium coli*, but is smaller ($40\ \mu$ long), has a more prominent mouth, and but one vacuole. It has been found in association with *Strongyloides*, *Ankylostoma*, and *Amæba*. Its significance is uncertain.

ANIMAL PARASITES AND MOLLUSCUM CONTAGIOSUM

Definition.—Molluscum or epithelioma contagiosum is an infectious disease of the skin marked by the appearance of white and pink papules.

Etiology.—The cause of this disease is, no doubt, a micro-organism of some sort. Its contagiousness is evidenced by the occurrence of epidemics in houses or asylums, by the occurrence of accidental inoculations, and by direct experiments. The incubation period seems to be a long one—sometimes extending to several months. The lesions have been found to contain small bodies whose resemblance to coccidia was long ago pointed out by Virchow. It is uncertain whether these are really parasites or epithelial degenerations. Some authors are positive regarding the parasitic nature of the bodies; others are equally convinced of their non-parasitic character. The most ably defended theory

for the parasitic nature of the virus ascribes it to an organism called *Strongyloplasma hominis*.

It has been shown that the virus is filterable, and many consider it should be placed among the Chlamydozoa. The large pale body, with the later appearance of internal structure, seen only by appropriate staining, strongly supports this view.

Appearances.—The disease occurs as single or, more frequently, multiple papules, at first quite small, but later becoming nodules of considerable size. In the larger a central depression or umbilication is seen, and on pressure cheesy matter may be expressed from this. After reaching about 3 or 4 mm. in diameter the papules remain stationary, or undergo softening and suppuration. In exceptional cases the tumor may reach the size of a small orange.

Seats.—This disease occurs on the face, neck, chest, genitals, or sometimes scattered over the whole body, sparing only the palms and soles. The lesions have occasionally been found on the mucous membranes.

Structure.—Microscopically, the lesions of this disease are found to consist of epithelial proliferations having a somewhat acinous arrangement, a hair-follicle occupying the center of each group of cells. The interior of the nodules is filled with soft, cheesy matter which may be expressed. The epithelial cells are arranged in several layers, the upper being normal cells with large nuclei, the deeper layers showing besides the nucleus, small droplets, or rounded spherules, the so-called *molluscum bodies*. These bodies grow in size and may be so large as to fill the cell, pushing the protoplasm and nucleus to one side. In this process the cell wall and protoplasm become horny, and practically the entire body consists of the enlarged molluscum corpuscle. Certain granulations and more or less definite segmentations within these bodies have been described as sporulating conditions. (See Skin.)

VERMES

TREMATODES, OR FLUKE-WORMS

The fluke-worms are usually flattened organisms, somewhat tongue shaped, and provided with powerful suckers and occasionally with hooklets. The intestinal canal begins in the oral orifice anteriorly, but is closed at the posterior extremity. Reproduction may take place directly or by the formation of an intermediate organism which is parasitic to certain lower animals. In this stage they are actively motile, swimming about in water, and are known as the cercariæ. Their action is irritative and obstructive.

FASCIOLA HEPATICA OR DISTOMUM HEPATICUM

The *Fasciola hepatica*, or liver-fluke, is from 15 to 35 mm. in length and 6 to 20 mm. in breadth; it is pointed at either end, and anteriorly is provided with two suckers, one at the head and one upon the ventral surface, somewhat posterior to the first (Fig. 142). The genital pore lies

between the two suckers. The eggs are oval in shape, 0.14 to 0.15 mm. in length, and provided with a lid at one pole.

The adult organism occupies the biliary ducts and is a frequent parasite of sheep. It is occasionally met with in man, usually occurring in considerable numbers. It gives rise to obstruction of the biliary passages and consequent enlargement, congestion, and later degeneration

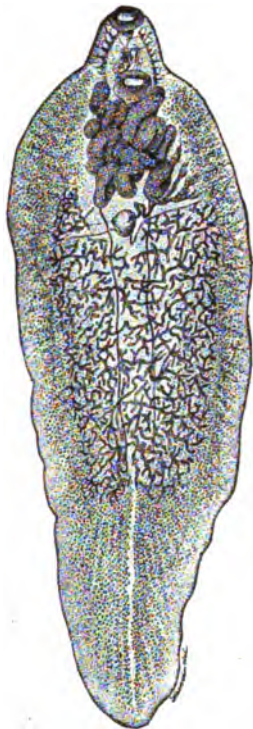


Fig. 142.—The common liver-fluke (*Fasciola hepatica*), enlarged to show the anatomical characters (after Stiles).



Fig. 143.—Ventral vein of a compressed specimen of a lung-fluke (*P. westermanii*) from a hog; greatly enlarged (after Stiles and Hassall).

of the liver. The gall-ducts above the point of obstruction have sometimes been found considerably dilated or cystic. Clinically, ascites and jaundice have been found, with gastro-intestinal symptoms and fasciola eggs in the stools.

DICROCELUM LANCEATUM

This form measures from 8 to 10 mm. in length and 2 to 2.5 mm. in breadth. The two suckers are far apart, and the genital pore lies between them. The eggs are 0.04 to 0.05 mm. in length and 0.03 mm. in breadth.

This parasite is frequently associated with the previous one, and occupies the biliary passages of sheep and cattle. It is occasionally met with in other animals and in man.

OPISTHORCHIS FELINEUS

This form varies in size with the degree of contraction, but is usually 8 to 11 mm. in length and 1.5 to 2 mm. in breadth. The two suckers are far apart, and the genital pore is just in front of the ventral sucker. The eggs are oval, operculated, measuring 0.03 mm. in length and 0.01 mm. in breadth, and contain a ciliated embryo when deposited. This parasite inhabits the gall-bladder and bile-ducts of the domestic cat in particular, but is also found in the dog, fox, and man. It has been observed in France, Germany, Russia, Holland, Italy, and Japan.

OPISTHORCHIS SINENSIS

This parasite resembles the *Opisthorchis felineus*. The length is 10 to 14 mm.; the breadth, 2.4 to 3.9 mm. The eggs are oval with a sharply defined operculum at the pointed pole; they measure 0.030 mm. in length and 0.017 mm. in breadth. This parasite inhabits the bile-ducts and gall-bladder of domestic dogs and cats as well as of human subjects. It is found frequently in Japan, also in China and India.

SCHISTOSOMUM HÆMATOBIUM OR DISTOMUM HÆMATOBIUM

This organism, sometimes called *Bilharzia*, occurs in sexually distinct forms, the male and female, however, occurring together. The male is 12 to 14 mm. in length and 1 mm. thick, and the body back of the large ventral sucker is somewhat flattened and curved ventralward to form a groove, in which the female is attached (Fig. 144). The latter is 16 to 18 mm. long, and 0.13 mm. thick. The eggs are 0.135 to 0.180 mm. long and 0.055 to 0.060 mm. broad, not operculated, and having a spine at one end or at the side of one end. The adult parasite occupies the portal vein and the veins of the spleen, mesentery, and the plexuses of the bladder and rectum. The eggs of the organism may be found in any of the organs, notably in the liver, in the intestinal walls, and in the mucous membranes of the urinary passages. They probably



Fig. 144.—*Schistosomum hæmatobium*, with eggs (von Jaksch).



Fig. 145.—Papillary thickening of the mucous membrane of the bladder, showing *schistosomum* eggs *in situ* (Mosler and Peiper).

occupy the vascular system ordinarily, but cause rupture of the walls of the vessels and thus escape into the tissues.

The pathological changes caused by this parasite and included in the term "bilharziasis" are more strikingly seen in the ureters and bladder in acute cases. Hyperemic spots or small hemorrhages may be seen in the mucous membrane, and the surface is covered with blood-stained mucus containing the eggs. In cases of longer standing roughness of the mucous membranes and usually small ecchymotic elevations or outgrowths, suggesting papillomata, are observed (Fig. 145). Section through these shows that they consist of proliferated cells with enlarged blood-vessels, from which the adult worm may be removed. The tissues surrounding the vessels may contain eggs in enormous numbers. The mucous membrane is frequently covered with a calcareous deposit composed of urate and oxalate of sodium, and the excrescences may be converted into calcified polyps. Among the final results may be cicatricial strictures of the ureter, pyelitis, and distention of the pelvis of the kidney, with atrophy of the kidney substance. Similar pathological processes may be found in the rectum. When the portal vein is occupied the eggs of the *Bilharzia* may be abundant in the liver substance. *Schistosomum hæmatobium* is a parasite occurring with enormous frequency in northern Africa and neighboring countries. It is comparatively rare in other parts of the world.

SCHISTOSOMUM JAPONICUM

Schistosomum japonicum, or *S. cattoi*, has recently been discovered in eastern Asia and Japan. This parasite inhabits the arterial side of the portal system. It is somewhat smaller than *Schistosomum hæmatobium*, and the male is distinguished by his non-tuberculated integument. The ovum has no spine, is regularly oval, perfectly smooth, and with a much thinner shell. It resembles closely the ovum of *Ankylostoma duodenale*. The ova are deposited in the mucosa and submucosa of the large and small intestine, especially the former. From here they escape with the feces. No more is known of the life-history from this point than is the case with the *Schistosomum hæmatobium*. It causes a peculiar kind of chronic enteritis and anemia, associated with enlargement of the spleen and liver, terminating in a fatal cachexia. Cats are susceptible to this parasite as well as man.

PARAGONIMUS WESTERMANI

This organism is from 8 to 10 mm. in length and from 5 to 6 mm. in breadth. The eggs are brownish, and from 0.08 to 0.1 mm. in length. The worm occurs in the lungs, occupying excavated spaces, usually near the periphery of the organ. These cavities contain reddish or quite hemorrhagic mucopurulent liquid and abundant eggs. The cavities are in communication with the bronchi, and clinically the disease is marked by cough and hemorrhagic expectoration or even repeated hemoptysis. The parasites themselves are rarely coughed up. The small tumors or burrows have also been found in the scrotum, liver, and brain.

In the brain they may give rise to grave nervous symptoms, often simulating those of intracranial tumor. This parasite occurs very frequently in Japan, China, and Corea, and has been observed several times in this country.

OTHER FLUKE-WORMS

Among other forms of fluke-worms of less importance are *Fasciolopsis buskii*, met with a few times in the intestine; *Cotylagonimus heterophyes*, *Agamodistomum ophthalmobium*, found in the lens of the eye; *Opisthorchis noverca*, occurring in the liver; and the *Monostomulum lentis*, occurring in the eye. The *Gastrodiscus hominis* occurs in the intestinal tract. Two forms, the *Hexathyridium venarum* and *H. pingucicola*, are possibly forms of encapsulated *Fasciola hepatica*. *Fasciolopsis rathouisi* is a fluke found in the intestinal canal of Asiatics.

CESTODES, OR TAPEWORMS

General Biology.—The life-history of the different forms of tapeworms is much the same. They have two states of existence, the *larval*, which is generally found in one species of animals (the intermediary host), and the *adult*, usually occurring in another species (the host). It is supposed that in the case of one or two tapeworms an intermediary host is unnecessary, but this is doubtful. The adult worm, or tapeworm (strobile), occupies the intestinal tract of man or the lower (vertebrate) animals. It consists of a *head* (scolex), by which the worm fastens itself to the mucous surface; and after the head, a *neck* of greater or less size and length, and a body consisting of separate *links* or *proglottides*. The latter represent complete organisms, containing a complicated genital apparatus, hermaphroditic in nature, which produces numerous eggs. The eggs are partly discharged from the segments in the intestinal tract through a *genital pore*, but especially escape into the outer world when the ripe segments are separated from the body of the worm, are discharged from the bowel, and subsequently rupture and scatter the contained ova (Fig. 146). The *egg* or *ovum* encloses an immature larval organism, which, when received into a suitable intermediary host, penetrates the walls of the stomach or intestine and finds its way to the muscles or organs, where it embeds itself and forms the well-known *measles* (Figs. 146 and 147). These are seen with the naked eye as small cyst-like bodies lying between the muscle-fibers. They contain a *scolex* or head, like that of the adult worm, inverted into a sac filled with clear, watery liquid. When the measles or *cysticerci* occur in hollow cavities, such as the ventricles of the brain, they may reach considerable size. They differ somewhat in different forms of tapeworm, as will be described in connection with the individual species. When flesh infested with larval tapeworms is eaten by man or some suitable animal, the cysts are dissolved and the scolex fastens itself upon the mucous membrane of the intestine. The body of the worm is then slowly or rapidly formed.

Man is the host of tapeworms of adult or of larval type, most frequently the former. In one case, the *Tænia echinococcus*, only the larval worm occurs in the human body, in the form of hydatid cysts.

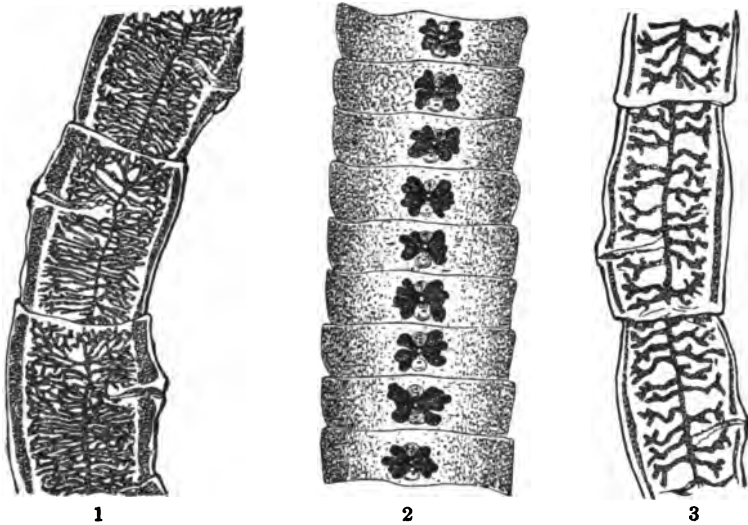


Fig. 146.—Segments of (1) *Tænia saginata*; (2) *Bothriocephalus latus*; and (3) *Tænia solium*, showing arrangement of uterus.

Pathological Physiology.—Adult tapeworms may exist in the intestines of man without causing disturbances of any kind. Frequently, however, digestive disturbances and pain and various reflex manifes-

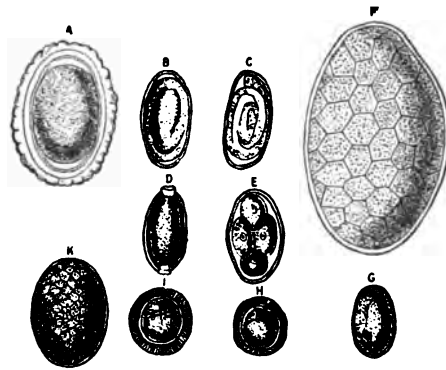


Fig. 147.—Eggs of various worms found in the alimentary canal of man: A, *Ascaris lumbricoides*; B, C, *Oxyuris vermicularis*; D, *Trichocephalus trichiurus*; E, *Ankylostomum duodenale*; F, *Fasciola hepatica*; G, *Dicrocoelium lanceatum*; H, *Tænia solium*; I, *Tænia saginata*; K, *Dibothriocephalus latus*; $\times 400$.

tations arise. These may be caused by the action of the worm as a simple foreign body, or may result from poisonous agents generated by the worm in its normal life, or as a consequence of death and degeneration of the segments. When there are many-worms (as in the case

of *Hymenolepis nana*) the disturbances of digestion may be largely mechanical; under similar circumstances, or when a single worm becomes coiled and forms a mass, intestinal obstruction may be occasioned. In the case of *Dibothriocephalus latus* poisonous substances are undoubtedly produced, and to these must be ascribed the severe forms of anemia caused by this worm. The toxic substance is produced by the worm and is within its body, but can be absorbed by the intestine. That such occurs is indicated by the precipitation reaction between blood of patients and extracts from the worm. The poison is a hemolytic lipid body. Other tapeworms rarely occasion anemia, and never the pernicious type just referred to.

TÆNIA SOLIUM

This form, sometimes called the pork tapeworm, occurs in the adult state in man as a worm 2 or 3 meters in length; and in the hog or rarely in man in its larval condition. The head is about the size of a pin-head and very dark. Anteriorly it has a rostellum armed with a double row of from twenty-two to thirty-two hooklets. At the sides of the head are four suckers (Fig. 148). Attached to the head is a neck of thread-like appearance, which terminates at once in the fairly developed segments of the anterior part of the body. The seg-



Fig. 148.—Head of *Tænia solium* (Moeller and Peiper).

ments at first are broad and short, but become longer in proportion to the breadth toward the posterior end. The sexually mature segments are found at the middle and the posterior end of the worm. They contain a uterus consisting of a median tube and six to twelve lateral branches (see Fig. 146, 3). The genital pore is found at one side of the segment, irregularly alternating in successive proglottides. The eggs, which may be squeezed from the segments or obtained free in the feces, are either oval or spherical, from 0.030 to 0.035 mm. in diameter, and consist of a peripheral striated zone and a central granular portion, showing indistinctly six lines representing hooklets (see Fig. 146). Groups of segments may be discharged from the bowel from time to time, but this is not frequent; the discharge of single segments is quite unusual. The proglottides have independent movement, and may sometimes be seen to move about upon the bed-clothes.

The cysticercus stage which gives rise to the *Tænia solium* lives normally in the intramuscular connective tissue and organs of the domestic pig, but it is known to exist also in a few other mammals as well as in man.

The Larval State in Man.—When the ova are taken into the stomach the shell is digested and the embryo with its six hooklets is set free.

This penetrates the wall of the stomach or intestine, and in some uncertain manner reaches the muscles or organs, where it effects a lodgment. The hooklets are discarded and a little cyst containing clear liquid is formed, and at one point may be found a bud-like projection into the sac. This develops a scolex or head, which eventually becomes identical with the head of the fully formed worm. The cyst may be surrounded by a wall of reactive connective tissue. The duration of this process of formation of the *cysticercus* varies somewhat (five to ten or twelve weeks). The size of the cysts in the muscles varies from minute points to that of a pea. In the ventricles of the brain the cysticerci may be as large as a small cherry. Occasionally compound or *racemose cysticerci* are met with.

In some cases the adult worm and the larval form have been found in the same individual (man). This is explained by the assumption that

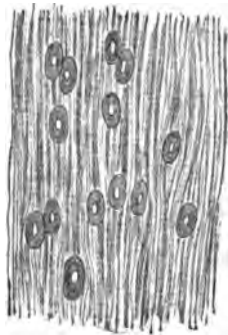


Fig. 149.—Measled pork; two-thirds the natural size (Leuckart).

the eggs have reached the stomach, where the larvæ have been set at liberty to penetrate the wall of the stomach and thus reach the tissues of the body.

Among the seats of special interest are the brain, the muscles, especially the peripheral muscles, tongue and heart muscle, and the subcutaneous tissues.

The Adult Worm in Man.—When measled meat (hog, occasionally that of deer, sheep, and other animals) is eaten in insufficiently cooked form by man the capsules of the cysticerci (Fig. 149) are dissolved, the scolex attaches itself to the mucous membrane of the small intestine, and the worm is developed. Usually there is but one worm; occasionally several occur in the same case. The worm may remain in the intestine for years, despite repeated efforts to dislodge it. In other cases it is spontaneously discharged. Reverse peristalsis may cause portions to be carried to the stomach, whence they may be discharged by vomiting.

Geographical Distribution.—The *Tænia solium* is an exceedingly rare parasite in America. It seems to be more common in certain parts of Europe.

TÆNIA SAGINATA

This form, sometimes called the beef tapeworm, is the common tapeworm of man. It is larger than the preceding form, being from 4 to 8 meters in length, though it may reach a length of 35 meters. The head is large (2 mm. broad), cuboidal, and provided with four suckers. There is an abortive rostellum, but no hooklets (Fig. 150). The neck is rather long and slender and the segments rapidly become broader than long, but in the posterior half of the worm, where the sexually mature proglottides are found, the segments are longer than broad. The uterus is formed like that of the *Tænia solium*, but the lateral branches are more numerous (twenty to thirty, and often di-

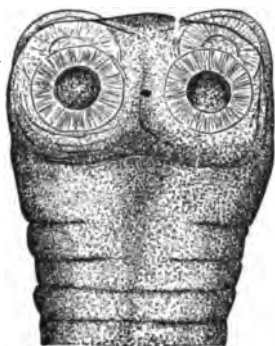


Fig. 150.—Head of *Tænia saginata* (Mosler and Peiper).

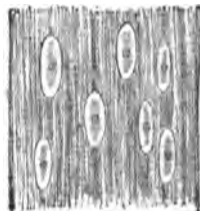


Fig. 151.—Cysticercus of *Tænia saginata*; natural size (Leuckart).

chotomously branched; see Fig. 146, 1). The eggs are rather more oval and larger than those of *Tænia solium*, but otherwise closely resemble the latter.

The **larval form**, or cysticercus, occurs in the ox and sometimes in the giraffe. The measles are found in the muscles, liver, lungs, and occasionally in other organs (Fig. 151).

The **adult form** occurs only in man, and occupies the small intestine. The presence of the worm does not seem to occasion any definite disease of the intestines, except in rare cases, when a number are found present in a coiled mass, or when one worm is similarly coiled. This may cause intestinal obstruction, and possibly in exceptional instances rupture of the bowel.

The symptoms ascribed to tapeworms are some of them doubtless reflex; but it is noteworthy that they are often absent until the patient discovers segments in the stools. (Further reference to possible pathological results is made in the discussion of *Dibothriocephalus latus*.) It is an exceedingly common parasite in certain countries (Africa and the East), but is more or less commonly found in all parts of the world.

There is probably no precipitin reaction in the blood, but a complement-fixing body has been found.

HYMENOLEPIS NANA

This form, sometimes called the *dwarf tapeworm*, in its adult state is 1 to 1.5 cm. in length (may reach 2.5 cm.) (Figs. 152 and 153). It has a rounded head, with a rostellum that may be protruded or retracted and that bears a single circle of twenty-two to thirty hooklets. The mature segments of the posterior end of the worm have a yellow color. The genital pore is on the same side in all the segments. The eggs are oval in shape, whitish and transparent; they are from 0.036 to 0.056 mm. long and 0.032 to 0.042 mm. broad.

The intermediary host of this form is not certainly known, but is supposed to be some form of insect or snail. In the rat the larval form occurs in the intestinal walls at the base of the villi in the form of a cysticeroid, which discharges its contained embryo into the intestine, where it matures. The same sequence may occur in man. The adult parasite alone



Fig. 152.—*Hymenolepis nana*, about natural size (Mosler and Peiper).



Fig. 153.—*Hymenolepis nana*, much enlarged (Mosler and Peiper).

occurs in man. The head attaches itself deeply in the mucous membrane of the bowel, and may cause considerable local disturbance. There are usually several or many worms associated; sometimes there may be several thousands.

HYMENOLEPIS DIMINUTA

This form (probably identical with *Tania flavopunctata*) is from 20 to 60 cm. in length; the head is elongated and verges gradually into the neck. The suckers are small, but there is neither rostellum nor hooklets. The segments are marked by a yellowish spot which represents the male genital organs. It seems to be commonest in children. The intermediate host is a species of small moth (*Asopia farinalis*). It has also been found in several other small insects.

DIPYLIDIUM CANINUM

This form is identical with the worm formerly known as *Tænia elliptica*, and is a common parasite of dogs and cats. The length is from 15 to 30 cm.; the head is provided with a rostellum bearing sixty hooklets ranged in four rows; the rostellum may be protruded or retracted. At the junction of the segments there is a considerable contraction of the diameter of the worm, giving the body a markedly linked character (Fig. 154). The mature segments have a reddish-brown color from the presence of the eggs. Each proglottis has a double sexual apparatus, with a genital pore at each side. The intermediary host is probably the louse of the dog and occasionally the flea. The adult worm usually occurs in numbers in the intestinal tract, and in some cases seems to produce inflammatory disturbances.



Fig. 154.—*Dipylidium caninum* (Mosler and Peiper).

DAVAINEA MADAGASCARIENSIS

This form is from 25 to 30 cm. in length; the head is marked by four large suckers and a rostellum bearing about ninety hooklets.

TÆNIA ECHINOCOCCUS

The *Tænia echinococcus* or *Echinococcus granulosus* in its adult form occurs in the upper part of the intestine of the dog, less commonly of the wolf and jackal, the larval condition occurring in man and in some of the lower animals. The mature worm is about 2.5 or 5 mm. in length, and consists of four segments (Fig. 155). The head, which constitutes the first, is provided with four suckers and a rostellum bearing two to four dozen hooklets in a double row. The second segment is about the breadth of the head, but somewhat shorter. The third is considerably larger; and the fourth is the largest of all, constituting about one-half or two-thirds of the entire worm. The uterus consists of a median portion with a few lateral branches. The eggs are oval, from 0.030 to 0.036 mm. in diameter, and the shell is rather thinner than in the eggs of other tapeworms.

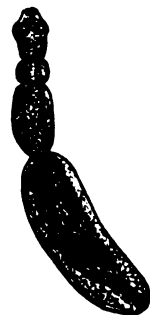


Fig. 155.—*Tænia echinococcus*, enlarged (Mosler and Peiper).

These eggs, deposited in water, or on vegetables, or conveyed by tactile communication from the body of the dog, are received into the mouth of man, and several of the lower animals and a few birds. From the stomach or intestine the embryo, liberated by solution of the egg capsule, bores its way into the vascular system, by which it may be conveyed to any part of the body of its host.

Echinococcus Cysts.—When the eggs reach the stomach or, more probably, the intestine of man the embryo is freed and penetrates the mucous membrane. From each egg a single scolex or several scolices

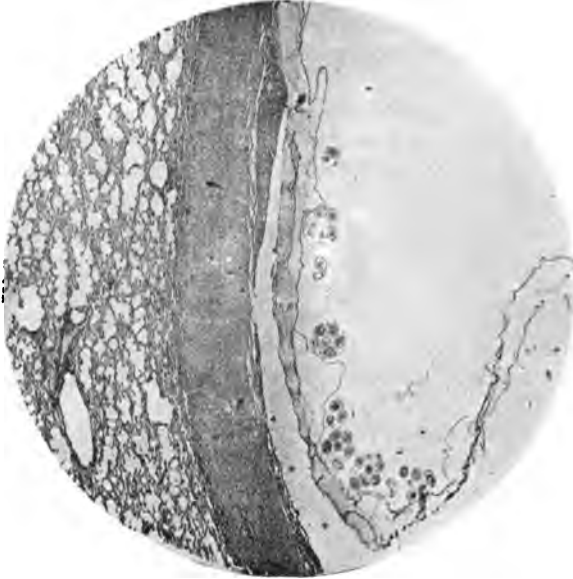


Fig. 156.—Finer structure of wall of echinococcus cyst, showing scolices in delicate cysts (from a specimen in the collection of Dr. Allen J. Smith).

may arise (Fig. 156). The scolex is carried by the blood or lymphatic stream to the liver or other organs, where it develops an *echinococcus cyst* (Fig. 157), of which there may be several varieties. The wall of the cyst



Fig. 157.—Echinococcus cyst of the liver (from a specimen in the Museum of the Philadelphia Hospital).

is composed of two layers, an outer cuticular and an inner parenchymatous, granulocellular layer. The whole is surrounded by an adventitious capsule of fibrous tissue derived from the organ of the host.

Within the cyst is a clear, limpid, sometimes amber-colored fluid, having a specific gravity of from 1009 to 1015, of neutral or alkaline reaction, and containing no albumin or only traces, but a considerable quantity of chlorid of sodium, cholesterol, and lipase have been found. A carbohydrate is sometimes found in the fluid. Hooklets are usually present and are of considerable diagnostic value. Such a cyst may increase in size, but with no alteration in its general structure, thus forming an *acephalocyst* (Lœnnec). This form is found in some of the lower animals and in cattle, where it may attain the size of an apple or an orange.

In other cases large numbers of small hollow "brood capsules" are formed within the internal space, in which the order of layers is just the reverse to what it is in the parent cyst, that is, they are lined inside by a thin cuticle and have the parenchymatous layer on their external surface. From the "brood capsules" the scolices or echinococcus heads develop as external protrusions, at the distal end of which the suckers and hooklets of the scolex are formed (Fig. 158). Some claim that the scolices may develop directly from the cyst wall without the medium of the brood capsules. To this form is given the term *Echinococcus veterinorum* or *E. scolicipariens*. It occurs chiefly in domesticated animals.

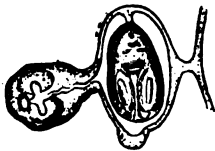


Fig. 158.—Formation of "brood capsules" upon the parenchymatous layer (Leuckart).



Fig. 159.—*Echinococcus multilocularis* (Luschka).

In man and only rarely in cattle the mother-cyst may develop "daughter-cysts," which, though smaller than the parent, resemble it in the structure of their walls, which are covered externally by a stratified cuticle and internally by the parenchymatous layer. They arise from small detached portions of the parenchymatous layer in the strata of the cuticle of the mother-cyst; they may bulge inwardly or outwardly and may separate themselves entirely from the mother-cyst. The "daughter-cysts" may remain sterile or may produce brood capsules and scolices or other cysts ("granddaughter-cysts"). To this cyst the term "hydatid," or *Echinococcus hominis* or *E. altricipariens* is applied.

There is another form of echinococcus occurring in man as well as in animals and termed *Echinococcus multilocularis* (Fig. 159). It varies from the size of a fist to a child's head, presents a collection of cysts from 0.1 to 5 mm. in diameter, and is embedded in a connective-tissue stroma. Each cyst is covered with stratified cuticle, and according to the size contains either solid cellular contents or a cavity lined with a parenchymatous layer. The fluid in this cavity may be transparent

or opaque, due to the presence of fat globules, bile-pigment if the cyst be in the liver, hematoidin, and fat crystals. The cysts are usually sterile, though scolices may be present in some. In man the center of the mass disintegrates, leaving a large cavity filled with a brown or greenish fluid containing shreds of the wall, calcareous bodies, small cysts, scolices and hooklets, fat, hematoidin, margarin, cholesterin, and concretions of lime. Nothing positive is known as to the development of this form, that is, whether it springs from a single oncosphere or from a number of oncospheres, or whether its conformation is brought about by peculiarities in its surroundings.

Echinococcus cysts may continue to grow until they have reached huge dimensions without undergoing any secondary changes. In other cases the parasite may die and the growth may cease, or active proliferation of the tissues around the cyst may lead to early destruction. In still other cases suppurative change occurs in the cyst or its wall. In all cases when the cyst reaches a certain size the tissues around it produce a connective-tissue capsule of greater or less thickness. When the parasite dies, inspissation of the liquid occurs, and it may eventually disappear or be converted into a thick whitish material; the cyst walls and the connective-tissue capsule at the same time shrivel and present peculiar concentric lamellations that are very characteristic. Eventually calcification of the wall of the cyst and, to a certain extent, of its contents takes place.

The blood of patients suffering from hydatid disease will fix the complement away from the hemolytic series if the contents of a cyst be used as antigen. This complement-fixation may be used diagnostically. The contents of the cyst seem to be toxic, for if they escape in the body a severe intoxication results, taking the form of local irritation, inflammation, fever, and urticaria.

Seats.—Echinococcus cysts are most frequent in the liver. They also occur in the lungs, kidneys, spleen, and omentum, and less frequently in the brain or other parts of the nervous system. The pathological effects are usually produced by direct mechanical pressure, but may be due to the toxin as noted above.

The **geographical distribution** is extensive, but the disease is common only in restricted localities, especially in northern countries (north of Europe, Iceland).

DIBOTHRIOCEPHALUS LATUS

The *Dibothriocephalus latus* is the largest tapeworm of man, reaching the length of from 2 to 9 meters or more. The head is flattened and club shaped and presents two groove-like suckers at its sides (Fig. 160). The neck is thin and gradually increases in diameter. The ripe segments are quadrate, and are distinguished by a rosette-like formation of the uterus, which is plainly visible in the center of each proglottis (see Fig. 146, 2). The genital pore is upon the flat surface of the segment and always upon the same side of the worm. The eggs are

oval in shape and enclosed in a shell presenting a hinged lid at one pole. The intermediary host is some form of fish, most frequently the pike. The eggs first undergo a certain amount of development in water, the embryo becoming free and floating about, or being propelled by a ciliated outer covering, and then entering the digestive tract of fish. Transmission of the parasite to its human host is believed to be confined to the eating of the flesh of infected fish imperfectly salted or cooked.

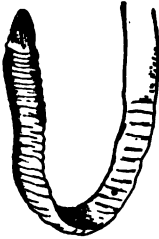


Fig. 160.—Head and neck of *Dibothriocephalus latus* (Leuckart).

The toxic effect of this worm is believed to be due to a hemolytic lipoid which is excreted by the worm or liberated by its enzymes when acting upon detached proglottides. Extracts of the worm have a marked digestive power on protein.

The **geographical distribution** is comparatively restricted. It is frequent in certain northern countries, as in Sweden and in parts of central Europe, especially in Switzerland. It is only occasionally met with in America in immigrants.

DIBOTHRIOCEPHALUS CORDATUS

This variety is much smaller than the last, the maximum being from 1 to 1.25 μ . The head is short, broad, and heart shaped, and the suckers are placed upon the flat surface. The uterine structure differs from that of *Dibothriocephalus latus* in being narrower and more elongated, and also in having lateral branches. The body of the worm contains granular calcareous matter. This parasite is found commonly in the seal, the walrus, and the dog in Greenland and Iceland, occasionally in man also. No doubt its larva lives in fishes.

BOTHRIOCEPHALUS MANSONI

This variety occurs only in the larval form in man, nothing being known of the character of the adult worm. It has been found in the region of the loins, in the urinary passages, and in the tissues about the eyes. The head of the worm is distinguished by a papilla-like projection.

DIPLOGONOPORUS GRANDIS

This parasite measures up to 10 meters in length. The scolex is unknown. On the ventral surface are two grooves in which lie the genital pores. The ova are brownish, oval, measuring 0.063 mm. in length and 0.048 mm. in width. It has been observed in Japan.

NEMATODES, OR ROUND-WORMS

ASCARIS LUMBRICOIDES

The *Ascaris lumbricoides*, or ordinary round-worm, is one of the most frequent intestinal parasites. The male may reach a length of 25 cm. and a thickness of 2 to 4 mm.; the female is longer, up to 40 cm., and thicker, up to 5 or 6 mm. The body of the worm is brownish or sometimes pinkish in color, and presents parallel ridges or rings somewhat like those of the earth-worm. The head is provided with three rounded prominences or lips, between which the mouth is placed (Fig. 161). The male shows two chitinous spicules at the cloaca. The eggs of the worm are produced in great numbers; they are elliptical, measuring 0.05 to 0.07 mm. in length, and 0.04 to 0.05 in breadth and are covered with a tough shell, surrounding which is a clear material in an irregular mass. The contents of the eggs consist of a granular material, sometimes showing the linear outlines of an embryo.

The ascaris develops in man from swallowing the eggs in infested drinking-water or food. The parasites may be present singly or in numbers. They occupy the small intestine, but frequently migrate, entering the gall-ducts, the stomach, the esophagus, and even the larynx or nasal cavities.

Pathological Physiology.—*Ascarides* may give rise to violent symptoms by obstruction of various passage-ways, and when in numbers or united in masses even intestinal obstruction may be caused. It is probable that ascarides produce irritating secretions, as it has been observed that considerable dermatitis sometimes arises in persons handling them. The toxic action has been ascribed to fatty acids and irritating volatile aldehyds which have been found in them. Occasionally abscess cavities containing lumbricoids are found in connection with ulcerations and perforation of the intestines. These abscesses were believed by older authors to be caused by the worms; at the present time it is more generally held that the worms play no important part, their presence being due only to their coincidence in the intestine.

ASCARIS CANIS

This form, which is common in cats and dogs, is rarely met with in man. It is much smaller than the ordinary round-worm, the male

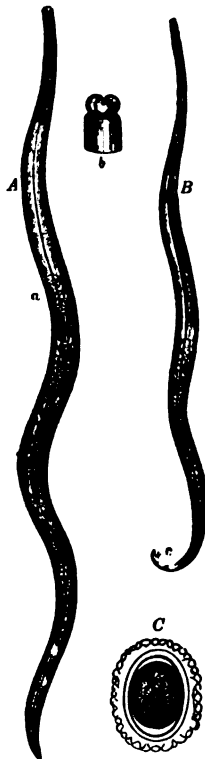


Fig. 161.—*Ascaris lumbricoides*: A, female; B, male; C, egg, magnified 300 diameters; b, head, magnified (after Perls).

reaching a length of 45 or 60 mm., and the female 120 to 130 mm. The head is distinguished by two lateral wing-like projections composed of chitinous material.

OXYURIS VERMICULARIS

The oxyuris, seat-worm, or pin-worm, is one of the commonest parasites of man. The male is 2.5 to 5 mm. in length; the female, 10 to 12 mm. (Fig. 162). The posterior end of the male is blunt and curved upon itself; in the female it is elongated. The eggs of the oxyuris, which are produced in great numbers, are oval or elliptical and about 0.05 mm. long. The embryo is visible within as a lobulated body. The parasite



Fig. 162.—*Oxyuris vermicularis*: a, female; b, male (Mosler and Peiper).

is developed directly from the eggs. When these are swallowed the outer coating is dissolved in the stomach and the embryos escape, to reach their full development in the small intestine. The impregnation occurs in the small intestine within a short time after the swallowing of the eggs. After impregnation and ripening the female parasites move toward the rectum and may be discharged, or may leave by their own movements. The life of the worm is short, but there is always the possibility of reinfection.

Oxyuris is especially common in childhood. It is probable that the worms sometimes cause inflammatory troubles. In cases in which they accumulate in numbers a form of verminous diarrhea may be produced.

In female children vaginitis frequently results from the migration of the parasites into the vagina.

TRICHINELLA SPIRALIS

This organism occurs in its larval form in the muscles or organs of man and in the lower animals; in the adult form it is found in the intestines of man or animals.

The adult male is about 1.5 mm. in length and 0.04 mm. in thickness. At the posterior end there is a retractile cloaca flanked by two projections. The female is 2 to 4 mm. in length and 0.06 mm. in thickness. The eggs are provided with a very thin shell, and the embryos escape from this within the uterus. They are produced in immense numbers. The young embryos found in the intestinal tract are from 0.1 to 0.16 mm. in length, the anterior end being thicker than the posterior.

In part they escape with the feces and die; the greater part penetrate the intestinal wall and are carried to various parts of the system, embedding themselves especially in the muscles, where they undergo further changes. Here the organism coils itself and becomes surrounded with a capsule, which is at first transparent, but

may subsequently undergo calcareous change and become opaque (Fig. 163).

Trichinellæ are acquired by man by eating improperly cooked ham. The capsules are digested and the larval trichinellæ set free. In the small intestine they reach their maturity in about three days; here impregnation takes place, after which the males die, while the females either bore more or less deeply into the villi or, by way of the glands of Lieberkühn, penetrate the mucous membrane, and so reach the lymphatic spaces, where they deposit their young. These are disseminated throughout the body by their own migrations or by means of the lymph- and blood-streams.

The favorite seat is the striated muscle tissue, and they lie within the muscle bundles themselves or, less frequently, between them. They reach their destination in ten days after the primary invasion, but subsequent crops are deposited as the young continue to mature in the intestines. In two or three weeks they begin to become encysted in the muscles, where they remain alive, capable of development for many years.

When the embryos are liberated in the stomach and intestines they occasion violent gastro-intestinal irritation, with vomiting, diarrhea, and often more or less pronounced collapse. In their later migration the worms set up intense muscular pains of rheumatoid character, with edematous swelling and fever. The disseminated disease is called "trichiniasis." The pathology of this condition includes, besides myositis and gastro-enteritis, fatty liver, nephritis, and infarcts. There is undoubtedly an irritative toxin produced, but whether this is wholly within the worm or in part made from the degeneration of muscle tissue is not certain. There is usually a marked eosinophile increase, the cells arising in the bone-marrow from toxin action. The worm uses the glycogen stored in the muscles during its growth. No passive immunity can be produced with the blood of injected animals.

Trichiniasis is common in all parts of the world, but has been largely reduced by greater care in the cooking of pork.

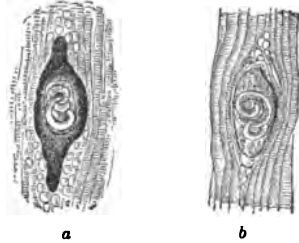


Fig. 163.—*Trichinella* capsule with its connective-tissue covering: a, early stage; b, calcified (Leuckart).

ANKYLOSTOMA DUODENALE OR UNCINARIA DUODENALIS

The *Ankylostoma duodenale* is a cylindrical worm, the female being from 12 to 18 mm. in length; the male, from 8 to 10 mm. The head is rounded, bent back like a hook, and is armed with six sharp, hook-like teeth, two pairs ventrally, one pair dorsally. The female is usually of a brownish or reddish color, due to the absorption of coloring-matter from the blood. The elliptical eggs are easily distinguished, from 0.056 to 0.063 mm. in length and 0.036 to 0.04

mm. in thickness. The shell is separated from the contents, and the latter have a granular appearance, are brownish, and in a state of segmentation. The eggs may appear in the stools in great numbers. If now they meet with the proper conditions, chief of which are a warm climate and damp earth, they hatch out and the active embryo is set free. It rapidly acquires organs of digestion and, after casting its skin several times and undergoing other evolutionary changes, is ready to re-enter a human host. Loos has proved quite conclusively that, while the organism may rarely enter the human alimentary canal by the mouth, the probable method of entrance is far more complicated.

After completing its exogenous phase of development, a suitable opportunity offering, the little worm penetrates the skin, generally of the feet and legs, of the coolies or others working in or passing through the contaminated earth in which the ankylostome ova had been previously deposited. The embryo enters the skin through some follicle, thence

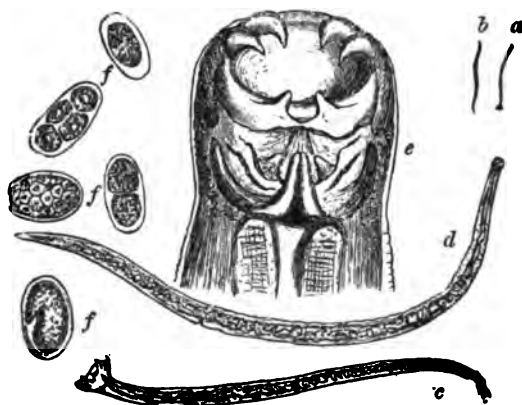


Fig. 164.—*Ankylostoma duodenale*: a, Male, natural size; b, female, natural size; c, male, magnified; d, female, magnified; e, head, greatly magnified; f, f, f, eggs (von Jaksch).

passes into a blood-vessel, and so is carried finally to the lungs. Here it leaves the blood-vessels and, undergoing further changes to enable it to resist the gastric juice, enters an air vesicle, passes to a bronchus, and so, by way of the trachea, esophagus, and stomach, finally arriving at the small intestine. Sexual characters are now assumed and reproduction commences, the ova falling into the contents of the gut and so passed out in the stools.

The adult worm may be present in small or large numbers, and is usually rather firmly attached to the mucous membrane. Changes in the latter, however, are not pronounced.

The method of entrance of the ankylostome to its human host throws important light on the condition known as "coolie itch" or "ground itch," which often is a forerunner of the intense anemia and other symptoms of the condition known as ankylostomiasis; "coolie itch" is a sort of papulopustular dermatitis generally attacking the

feet and legs, and at times other surfaces as well, of the coolie laborers on plantations. It is probably caused by the passage of the ankylostome embryos through the skin. Ankylostomiasis or uncinariasis is characterized by severe and intense anemia, abdominal discomfort or pain, general wasting, often followed by death. This parasite was also found in many cases of Egyptian chlorosis, and was the cause of the intense anemias (pernicious anemia) of the laborers engaged in building the St. Gotthard tunnel.

NECATOR AMERICANUS OR UNCINARIA AMERICANA

This parasite is shorter and more slender than the *Ankylostoma duodenale*, the male being 6 to 9 mm. long, and the female 8 to 15 mm.



Fig. 165.—A, Dorsal view of head end of *Ankylostoma duodenale*; B, dorsal view of head end of *Necator americanus*. (Drawn to scale to show difference in size. A. J. Smith.)

long. There are also minute differences in the head and body, though the general structure of the two parasites is the same. In place of the

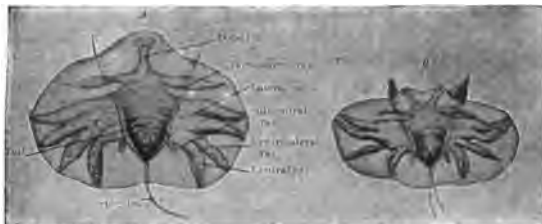


Fig. 166.—A, Caudal bursa and tail of male *Ankylostoma duodenale*; B, caudal bursa and tail of male *Necator americanus*. (Drawn to scale to show difference in size. A. J. Smith.)

ventral and dorsal oval teeth there are plates or suckers, while deep in the mouth opening there is one central tooth and one pair of narrow



Fig. 167.—Ova of (A) *Ankylostoma duodenale*; (B) *Necator americanus*. (Drawn to scale to show comparative size. A. J. Smith.)

straight teeth ventrally and dorsally. The ova are larger than those of the *Ankylostoma duodenale*, being 0.068 mm. in length and 0.038 mm.

in breadth, otherwise they are similar. This form has been found especially in tropical and subtropical America and in the West Indian islands. The conditions produced by the American hookworm are similar to those caused by the Old World form, but are probably less intense.

The pathological effect of uncinariasis is toxic. The worms remove some blood from the gut wall for their nourishment, but not enough to cause the severe anemia of the disease. Small hemorrhages appear in the gut. A weak hemolysin is formed, can be extracted from the worm, and is probably absorbed by the intestine. There is also an active coagulating body in the head of the dog hookworm. There are to be found in the body fatty degeneration and hyperplasia of the bone-marrow.

STRONGYLOIDES INTESTINALIS

This parasite occurs in two generations or types: the parasitic, in which the individual of female habitus represents both sexes and reproduces by parthenogenesis; and the free living generation, in which the two sexes are represented by different individuals. The parasitic generation (*Anguillula intestinalis*) lives in the upper intestinal tract, boring deeply into the mucous membrane and frequently into the epithelium of Lieberkühn's glands both for nourishment and oviposition. This form is 2.2 mm. in length and 0.034 mm. in breadth; the mouth is surrounded by four lips, the esophagus is almost cylindrical and a quarter the length of the entire body; the eggs measure 0.050 to 0.058 mm. in length and 0.030 to 0.034 mm. in breadth. The eggs develop in the intestinal wall, and the rhabditiform larvæ, which measure 0.2 mm. in length, reach the lumen of the intestine and grow to double or three times that size until they are passed out with the feces. With the proper temperature (26° to 35° C.; 78.8°-95° F.) they develop in about thirty hours into the free living generation (*Anguillula stercoralis*). This form is sexually differentiated; its body is smooth and cylindrical, with pointed tail end. The mouth has four distinct lips; the esophagus is short with a double (rhabditic-like) dilatation; there are three small curved spicules at the base of the tail. In the males the posterior end is rolled up, in the females it is straight and pointed. The males measure 0.7 mm. in length and 0.035 mm. in breadth. The females measure 1 mm. in length and 0.05 mm. in breadth. The ova are thin shelled, yellowish, and measure 0.07 mm. in length and 0.045 mm. in breadth. The embryo as it emerges from the egg often within the uterus measures 0.22 mm. in length and resembles the parent form. After growing to about 0.55 mm. in length it moults and then takes on the characteristics of the parasitic form (strongyloid or filariform larvæ). In the European strongyloides the free living generation is absent. This may also be true in the strongyloides of tropical origin where external conditions are unfavorable to the development of the rhabditic form.

There are, as has been mentioned, two methods of reproduction: that by direct transformation of the rhabditiform larvæ into filariform

and then into adults, and the indirect, through the intermediate generation. By this arrangement the parasite may reproduce directly if external conditions are unfavorable, and indirectly when conditions are favorable. The latter method seems to be more common in the tropics than in colder countries. The adult form alone is parasitic in the true sense; the other form representing only a stage for the perpetuation of the species. Unlike the ankylostome, eggs of strongyloides are rarely found in the stools excepting after purgation. Infection probably occurs through tainted water and food, but some experiments seem to indicate that the embryo may penetrate through the skin and thus gain access to the body.

Strongyloides is common in tropical countries, and was first discovered in cases of Cochin China diarrhea. It is probably capable of causing intestinal irritation, and seems rarely present in healthy persons, but its pathogenicity is still uncertain. It has recently been discovered in the United States.

TRICHOCEPHALUS TRICHIURUS

The anterior portion of this parasite is thin and thread-like, while the posterior portion is thicker. The length of the worm is from 4 to 5 cm., the male being somewhat the smaller. The thicker part of the male is curled upon itself and blunt at the end, while that of the female is straight and more pointed (Fig. 168). The eggs are very characteristic, being brownish in color, covered with a thick capsule, and having at either pole a button-like projection (see Fig. 146, D). The egg is 0.050 to 0.054 mm. in length and 0.023 mm. in breadth.



Fig. 168.—*Trichocephalus trichiurus*; natural size: a, Female; b, male (Heller).

The parasite, commonly known as the "whip-worm," occupies the cecum in man, occasionally the vermiform appendix, and sometimes the small intestine. It is one of the most common intestinal parasites in this country and appears to be well distributed over the entire surface of the globe, being particularly frequent in children in Syria and Egypt. It does not, as a rule, produce serious disturbance, but may cause intestinal or reflex nervous symptoms. Recently it has been claimed that the parasite causes considerable disturbance by abstracting blood and producing a soluble toxin.

FILARIA MEDINENSIS

The *Filaria* or *Dracunculus medinensis* is a round-worm infesting the subcutaneous tissue and the skin. The male has not been recognized with certainty, though two observers have found a smaller degenerated and partly calcified form in association with the female filaria. The female sometimes reaches a length of 50 to 80 cm.; it is

yellowish in color and exceedingly elastic; the anterior extremity is roundish, the posterior terminating in a spine. In general appearance it resembles a string of catgut. The body of the worm contains a highly developed uterus, which practically fills the cavity of the worm, the intestinal tube being crowded to one side. The uterus is found to contain innumerable small embryos; these escape when the parasite is ruptured.

The process or place of impregnation is unknown. When ovulation, however, is completed the parasite moves down to the leg or foot of her host, whence she will be better able to deposit her young in water, which is absolutely necessary for their development. Here she drills a small hole in the derma, but does not penetrate the epidermis. Over this a small blister or bulla forms which soon ruptures, disclosing the small opening in the center of a superficial erosion. When the host now enters the water a portion of the uterine tube is forced out through the mouth of the worm by the contraction of the musclocutaneous integument and ruptures, setting free myriads of the embryo worms. This is repeated at intervals until the entire uterus is expelled and parturition is completed. This takes, as a rule, two to three weeks. The worm now dies, and is expelled or pulled out bit by bit or entire, with or without suppuration. Forcible attempts at removal of the worm from the tissues may result in its rupture, thus setting free millions of embryos in the tissues, whose presence, associated with suppuration, which usually follows, results in a condition of considerable danger to the patient. It is, therefore, better to wait until parturition is completed before attempting removal of the worm.

The embryos having been deposited in the water take up their abode in the intermediary host, the body cavities of a species of cyclops. They enter by penetrating the delicate membrane that unites the plates of the ectoskeleton of the crustacean. The life-history from here on is a blank. It has been thought that after proper development the parasite is swallowed in drinking-water while still in the body of the crustacean, or it may be after it has escaped from this intermediary. Or it may obtain entrance to its human host by boring its way through the skin.

The organism occurs very abundantly in tropical countries of the Old World, notably Arabia, along the coast of the Caspian Sea, in Abyssinia, and Guinea. The parasite is sometimes called the Guinea-worm.

FILARIA BANCROFTI

Several varieties of filariæ have been found in the blood and are included under this generic term. The discovery of the organism or, rather, of the embryos was made by Wucherer in a case of hematuria.

The embryos of *Filaria bancrofti* or *F. sanguinis hominis* appear in the blood, urine, the lymph, and the tissues as thread-like structures, varying in size in the different varieties. The ordinary form has a thickness of about the diameter of a red corpuscle, and is as much as

0.13 to 0.3 mm. in length. It consists of a transparent sheath, almost completely filled with the embryo, the ends, however, projecting a little beyond the organism in a sac-like fashion (Fig. 169). The embryo is actively motile, squirming, thrashing, or curling and uncurling itself rapidly, and thus producing more or less agitation of the corpuscles or solid bodies in its vicinity.

The number of the embryos found in the blood varies greatly; in many cases a search through several cover-glass preparations may be necessary to detect a single one. Usually they are more abundant. A feature of importance is that they occur only during the night, unless the patient reverses the usual conditions and rests during the day.

The adult worms occupy the lymphatic channels, the male and female being found together. The male is colorless and measures about 40 mm. in length and 0.1 mm. in thickness. The cephalic extremity is a little thickened, the posterior extremity is bent and rounded, but not spiral. The female is brownish, 76 to 80 mm. in length and 0.2 to 0.3 mm. in thickness. Both extremities are rounded. Almost the entire body

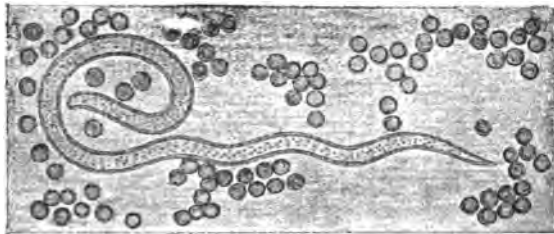


Fig. 169.—Filaria embryo, alive in the blood (F. P. Henry).

is occupied by the two uterine tubes, in which may be seen the ova and already developed larval filariæ. These enter the circulation and are discharged in various ways, especially in the urine. The common tropical mosquito (*Culex fatigans*) has been found to act as the intermediary host in which the embryo reaches its fuller development. The embryo filariæ are taken into the midgut of the mosquito together with a certain amount of blood at a time when the filariæ are found in the peripheral circulation. Here in the thickened plasma the embryos are able by their active movements to break through their sheath. Now, by means of a short delicate spine and a circle of hooked lips at the head end, the organism bores its way to the thoracic muscles of the mosquito. Here in the course of one to three weeks it goes through a series of changes and increases considerably in size. It now works its way to the head of the mosquito, and finally passes down into the labium or sheath of the proboscis, where it awaits the opportunity to enter a human host when the mosquito next feeds on man. It then finds its way into the lymphatic trunks, where the sexes come together and the young are born.

Filariasis is particularly common in the warmer climates, but is occasionally met with in this country, especially in the Southern States. One of its most frequent forms is characterized clinically by *hemato-chyluria*. The embryos in these cases may be found in the blood and also in the chylous urine. Pathologically, no gross changes may be found, but there may be in other cases evident distention of the lymphatic channels and blood-vessels of the pelvis of the kidneys, ureters, or bladder; and the embryos may be found in the substance of the kidneys or in the walls of the blood-vessels. Another form of filariasis is *elephantiasis*. In these cases there is obstruction of the lymphatic vessels in consequence of the presence of the parasites, of thrombi, or of inflammatory lesions, and as a result of these conditions dilatation of the peripheral lymphatic vessels occurs. The skin may be ruptured and chylous liquid may exude. The embryos may be found in this on microscopical examination.

Varieties.—Manson has described three varieties of embryonal filariæ—the original form, or *Filaria nocturna*; a second variety, in which the embryos are found at any time, night or day, called *Filaria perstans*, characterized also by its small size (0.2 mm. in length), great motility, and absence of a sheath; this he believes is the cause of certain skin diseases (craw-craw) of Africa; the adult worm is unknown. The third form is the *Filaria diurna*, which appears in the blood only during the day. The last is probably the embryo of *Filaria loa*, a wandering form frequently occurring in the eye, lying under the conjunctiva. It is found in Africa and tropical America. Manson believes that the mangrove fly is the intermediary host.

OTHER FORMS OF FILARIÆ

The *Filaria lentis* was found in the lens in a case of cataract; the *F. labialis* was discovered in a pustule on the lip of a student in Naples; the *F. hominis oris* was found by Leidy in the mouth of a child; and *F. restiformis* was found in the urine of a patient by the same observer. The *F. immitis* is the common filaria of the dog, and has been found in man. The *F. ozzardi* was found in the blood of Caribs of British Guiana. The *F. loa* is confined to Western Africa. The *F. bronchialis* was found in the bronchial lymphatic glands in a case of phthisis, and has also been found in the trachea and bronchi. The *F. demarquayi* and *F. magalhæsi* are forms whose identity has not been sufficiently established. *F. conjunctivæ*, *F. lymphatica*, and *F. romanorum-orientalis* are others that have been described.

ECHINORHYNCHUS GIGAS

This is a large round-worm, the body being marked by distinct, transverse, parallel rings. The male may be from 7 to 10 cm. in length, the female from 31 to 50 cm. There is a retractile rostellum, with six rows of hooklets at the anterior end, each row composed of eight spicules. The parasite occupies the small intestine of the hog, and has been found

occasionally in man. The intermediate host seems to be the grub of the cockchafer and the June-bug.

Other varieties of *echinorhynchus* have been described, but are not well-determined species.

EUSTRONGYLUS GIGAS

The female of this species may reach a length of 1 meter; the male is but one-third the size. The anterior end of the worm is retracted and the mouth surrounded by six papillæ. The posterior end is expanded and provided with a spicule projecting from the cloaca. The color of the worm is brownish or blood red. The parasite is found in the pelvis of the kidneys, ureters, and bladder of dogs, horses, cattle and other animals, and rarely in man. Among its results are enlargement of the pelvis of the kidney and atrophy of the kidney substance.

STRONGYLUS APRI

This parasite was found in the lungs of a child. It resembles the strongylus met with in the lungs of sheep and other animals.

STRONGYLUS SUBTILIS

This organism has been described by Loos as being found in the intestines at autopsies of natives of the Egyptian lowlands.

ANNELIDES

Two forms of leeches are of some pathological importance. The *Hirudo ceylonica* is a form occurring with great frequency in Ceylon and other islands, and in parts of South America. It is found in vegetation, and attaches itself to the skin of the legs and to other parts of man by means of a sucker and its short teeth. It may give rise to painful ulcerations when removed. The *Hirudo vorax* is met with in parts of Europe and Africa. It gains access to the mucous membranes of the mouth, larynx, trachea or nasal chambers, and leads to inflammatory troubles. It is not able to effect a lodgment upon the skin.

ARTHROPODA

A number of parasites belonging to the groups Arachnoidea and Insecta are met with in man. Most of these, however, are purely external parasites, and are fully described in works upon diseases of the skin. There are two forms, however, that merit brief description here: the *Linguatula rhinaria*, its larval form of *Pentastoma tenioides*; and the larvæ of various flies, the presence of which in the gastro-intestinal tract and other parts of the body is termed *myiasis*.

LINGUATULA RHINARIA

This parasite is occasionally found in the liver, and rarely in the spleen, intestinal walls, lungs, and kidneys of man. It is discovered in small nodular lesions, which consist of the more or less degenerated parasite lying in a cheesy or semicalcified material, surrounded by a fibrous or calcareous capsule. The parasite is from 4 to 5 mm. in length and 1.5 mm. in breadth; has a rather rounded body, which is encircled by parallel rings armed with spicules; and is provided with two pairs of stout chitinous hooklets, one pair lying on either side of the mouth. The adult form, *Linguatula rhinaria*, resembles its larva in structure, but is considerably larger, the male being from 16 to 18 mm. long, the female from 80 to 100 mm. This form lodges in the nasal cavities and frontal sinuses of the dog and other animals, and produces eggs containing the embryos, which escape with the nasal secretion and eventually gain access to the alimentary tract of other animals or of man.

POROCEPHALUS CONSTRICTUS

This species has been discovered in man in a few cases, and only in its larval form. It differs from *Linguatula rhinaria* in being larger (10 to 14 mm. in length) and having a smooth surface. It has been found in the peritoneal cavity, intestines, liver, and lungs.

MYIASIS

A number of flies, of the orders Estridæ, Musca, Lucilia, and Sarcophaga, may deposit their eggs in wounds or in cavities of the body to which they gain access, such as the nasal or pharyngeal chambers and the communicating passages. The eggs so deposited are hatched, and the larval insects may be retained and may occasion intense irritation. Sometimes the larvæ are found in the gastro-intestinal tract, the eggs having been swallowed with food. Immense numbers may be discharged from the intestines, and in some cases the larvæ seem to occasion intestinal irritation. The term *myiasis* is given to the invasion of these larval insects.

CHAPTER XI

THE METHODS OF TRANSMISSION OF THE COMMUNICABLE DISEASES

THE acquisition of a communicable or infectious disease requires the entrance into the animal or human body of the disease-producing agent, which must exist in nature in a form which can be conveyed to or into the body. The paths of infection have already been discussed, and it remains to be considered here how the viruses are brought to these paths. Sanitarians have supplied data which permit the classification of the transmission of disease as direct, indirect, and through an intermediate host in which the virus must pass through some cycle of development. There are some diseases whose method of propagation is not yet known, and these will be discussed separately.

The sources from which diseases are disseminated are human beings and lower animals. There are a few conditions, like ergot-poisoning and pellagra, exhibiting a clinical and pathological course much like an infection, which seem at this time to be traceable to the vegetable kingdom.

The diseases that pass from human being to human being far outnumber those contracted from animals, and many are truly specific for man; for example, the acute exanthemata are diseases of the human race alone, and only very exceptionally can be transmitted experimentally to the lower races. As a natural corollary it follows that man is the greatest disseminator of infectious disease among men. Many infections more or less specific for the lower animals are transmissible to man, but do not, as a rule, assume epidemic forms; while acute infections peculiar to man and spread by him tend to appear epidemically or endemically. In like manner, animals are the most important means of dissemination of infection among animals.

The transmission of disease from man to man occurs by direct contact, such as handling or kissing; indirectly, as in the use of infective linen, eating utensils or taking infective material into the mouth, or by an intermediate host, as the mosquito in malaria.

From animals men are infected chiefly by handling or by the partaking of infected milk or meat. Biting is of great importance, as exemplified by rabies. Man is infected by plants usually by eating, but simple handling of some plants, like poison ivy, produces a condition akin to infection in susceptible persons. Diseases are propagated among animals chiefly by direct contact or by infective food. When one animal of a herd or flock becomes infected it is easy for it to infect the common food supply, be it pasture, crib, or pan. The importance of this lies in the fact that a milk-giving herd may be infected throughout by one new member and render the milk unfit for human use.

Direct Infection.—*Contact Infection.*—This group embraces those diseases which demand for their dissemination a rather intimate personal relation of the sick and well, either by touching or the intervention of air or droplets in the expired air. It is doubtful if any infection is transferred in this manner only, but certain diseases are so contracted in the vast majority of cases. For example, the venereal diseases—lues, gonorrhea, and chancroid—are practically always acquired by the introduction of the germs into skin or mucous membrane abrasions by direct inoculations from infected persons. Their causative organisms survive exposure to conditions outside the human body for a very short time. Drying is fatal to the *Spirochæta pallida* and the *gonococcus* in a few hours. Chicken-pox is an acute infection that seems at the present day only transmissible directly, that is, it is not carried by a third person. Rabies is a good example of direct infection, for it is obligatory that the fresh virus be introduced beneath the skin. While the exact means of transmission of leprosy is not known, it is probable that direct contact is necessary for its acquisition.

Aside from these contact infections, direct transmission is air borne by the dissemination of bare germs or those contained in finely divided droplets of sputum or saliva, or carried in dust. It is to be emphasized that no sharp line can be drawn between direct and indirect transmission, because all those diseases which may be carried by fomites and food can be acquired by the direct passage of infective matter from the sick to the well. There are some infections, like diphtheria, scarlatina, mumps, small-pox, and measles, whose spread is possible merely through the air and yet can be carried by fomites and by a third person, possibly by a "carrier" (*q. v.*). These may be called the air-borne infections when emanations from the sick person are carried to the well merely through the air. The exact course of travel is not known for those diseases whose causative agent has not been isolated, *e. g.*, small-pox. In the bacterial diseases, like tuberculosis, diphtheria, pneumonia, plague, influenza, micro-organisms are loosened from the patient's person by coughing, or the drying of secretions or excretions, and blown about by air currents. They may settle upon surfaces, whence they are again carried to the well by air or contact. The most important factors in dissemination of bacteria by such means are coughing and sneezing, which forcible expiratory actions project infective matters considerable distances. It is said that tubercle bacilli may be thrown twenty feet in front of a coughing consumptive. Few, if any, micro-organisms are to be found in the breath during quiet respiration. The bacteria are carried by droplets of sputa. These fall and dry upon surfaces, to be pulverized and removed by air or contact. Dust is also a carrier of germs and serves as a protection for them, as it keeps away light. The viruses of communicable diseases are for the most part quickly destroyed by exposure to direct light, but if protected by some envelope, as mucus about a tubercle bacillus, their infectivity is indefinite. Disease germs are common in dust and dirt that dry upon floors and walls of public conveyances. In public places or conveyances, houses, hospitals, schools,

and workshops this sputum and dust transmission is of great importance. Bacteria are not widely disseminated by air currents, since they soon perish by exposure. They are not carried far by air currents from sewers or drains, notwithstanding popular belief to the contrary. Bacteria may be propelled several feet by the bursting of bubbles in a sewer opening, but this is of little or no importance in the transmission of disease.

Indirect Transmission.—This takes place when the agent passes from the sick to the well by some conveyance which permits the virus to grow or at least to sustain life. The vehicle may be water, food, soil, insects or human beings, or more passive carriers, called fomites, like infected bed or body clothing, towels, drinking cups, and eating utensils. In these transmissions we assume that the germs are simply carried by the vehicle as a passenger and that the vehicle itself exerts no influence upon them. By a prolonged existence in the vehicle and, therefore, absence from the human body, the pathogenic organisms may become reduced in virulence.

Water transmission, according to present knowledge of disease, is confined to typhoid, cholera, and perhaps dysentery, both of the bacillary and amebic type. No definite limit can be set for the life in water for the germs of these diseases, but it may be months.

Food Transmission.—The most important food-carrier of disease is milk. Typhoid fever, diphtheria, septic sore throat, and scarlatina are carried by milk when contaminated during collection and distribution by persons suffering from these diseases or by carriers. Infected water used to wash cans or to dilute milk may introduce typhoid bacilli. Diseases originating in the animal supplying the milk, as tuberculosis, foot-and-mouth disease, and Malta fever, are transmissible to man. The transmission of tuberculosis by milk of tuberculous animals cannot be doubted.

Vegetables convey disease only when contaminated by surroundings in cultivation or in the process of preparation for food. Oysters and other shell-fish when taken from polluted water may convey typhoid fever and cholera. Meat conveys animal parasites and acute bacterial and toxin diseases like paracolon and paratyphoid fever, botulism, and ptomain-poisoning. Tuberculosis is undoubtedly transmissible by infected meat.

Soil Transmission.—There are many organisms in soil, but few of the varieties are pathogenic for man. Certain pathogens, like typhoid and plague bacilli and cocci, are occasionally to be found, but are of little importance in hygiene. In plague centers the soil is said to be frequently infected with plague bacilli. The organisms most frequently found in the soil that produce specific infections in man are those of tetanus, anthrax, malignant edema, and symptomatic anthrax. The life of these germs in soil is favored by their spore formation.

Insect Transmission.—This may be direct or indirect. The former includes those transmissions in which the insect acts as an intermediate host of the virus, permitting some developmental phase in it,

a subject to be considered later. Indirect or mechanical transmission occurs when the insect becomes infested with human pathogens and carries them passively to situations where they can infect human beings. Thus, flies may carry typhoid bacilli upon their bodies from dejecta to food; fleas transfer plague bacilli from human cases or infected rats. There is a class of disease transmitted by biting insects in which it seems that the virus does not pass through a cycle of development in the body of the insect. The virus remains in an infective condition within the intermediate host for various lengths of time and may be transmitted to the young. In this class may be included typhus, relapsing fevers, Rocky Mountain fever, and trypanosomiasis. It may be found later that a cycle of development occurs in these insect bearers.

Animal Transmission.—Animals may act as passive carriers of such diseases as diphtheria, scarlet fever, or measles by association with infected persons. The cat is one of the commonest of such conveyors; it is frequently responsible for the spread of the mycosis *farus*. Animals act as active carriers of various worms. Certain diseases, like actinomycosis, may be transmitted to man by animals.

Human Transmission.—Human beings transfer infection in one of three ways: (a) when actively suffering from disease; (b) passively from sick to well upon person or clothing, and (c) as "carriers." The operation of the first and second methods is obvious; it is to be understood that under the second heading the conveying person is not ill with the disease he is transmitting. "Carriers" are persons who having suffered with a disease have not destroyed or discharged all the virus from the body when recovery took place. This virus has remained in some locality protected from the action of the blood-serum, or by long sojourn in the body has become immune or "fixed" or "fast" to the bodily defenses. Under certain circumstances it may leave the body and infect others. Thus, after typhoid fever, typhoid bacilli may remain in the alimentary tract for years, passing out with feces and contaminating surroundings or the water and food supply. This also occurs after cholera and diphtheria; in the latter case Klebs-Löffler bacilli remain in the throat a long time. These persons might be called "chronic carriers," while the persons who merely passively transfer infection might be termed "accidental carriers." During an infectious disease the patient is, of course, a carrier, and might be spoken of as an "infected carrier."

Transmission by inanimate objects or fomites is purely mechanical. It is of importance in all infectious diseases except those only transferred by insects.

Insect Transmission with a Cycle of Development in the Intermediate Host.—This is a group differing from the indirectly insect-borne diseases, in that a period of time must elapse between the reception of the virus in the body of an insect until it becomes infective for man. The diseases whose transmission by this means seems now proved beyond doubt are malaria, yellow fever, filariasis, and dengue. Mosquitoes are the "intermediate host" and man is called the "definitive host." Ticks,

flies, and other insects also transmit disease and may permit some form of development, but this is not yet proved.

Despite the fact that in all insect-borne diseases the viruses do not have the same biological history, there are many analogies among them. The insects concerned are biting or suctorial, and include mosquitoes carrying the viruses above mentioned; ticks, transmitting relapsing fever, Rocky Mountain fever, and tick fever; flies, transmitting trypanosomiasis; and lice, believed to convey typhus.

The viruses of yellow fever, dengue, and the tick fevers have not yet been isolated, but epidemiologically their connection with insects is well established. The insect transmitting African relapsing fever is known, but the other forms are still in doubt. (See page 339.)

These insect-borne diseases are transmitted always by the same species of intermediate host, and the virus seems specific for species in the definitive host. One insect seems to carry only one form of virus. The contagium does not harm the carrier so far as known. The diseases appear only where their respective insects live, and when they spread it is the definitive host which carries them, since the insects do not travel far. These infections are not directly communicable. There is a definite and quite constant incubation period peculiar to each disease for both the intermediate and definitive host. Ticks are the only ones that transfer the virus to their young.

Method of Transmission Unknown.—In this class only one disease is of importance—poliomyelitis. This acute infection appears and spreads in a manner which baffles investigation. The following theories have been offered to explain the spread of infantile paralysis:

1. That it is passed from person to person via the nose and throat, these localities being constant seats of the virus and the most probable infection atriium; that it is carried in the nose or upon the person by hidden or abortive cases or by an accidental carrier.

2. That it resists conditions outside the body long enough for it to pass through the air long distances, and to remain virulent in dust.

3. That it is transmitted by insects. Rosenau showed that the disease can be transmitted from monkey to monkey by the bite of the stable fly (*Stomoxys calcitrans*).

None of these theories cover all cases. It is certainly not easily transmitted by direct contact, because frequently only a single member of a large family of children may be affected.

PART II

SPECIAL PATHOLOGY

CHAPTER I

DISEASES OF THE BLOOD

ANATOMY

THE blood is a liquid tissue composed of corpuscles or cells and a fluid intercellular substance. The cells are of three kinds: the red corpuscles, or *erythrocytes*; the white corpuscles, or *leukocytes*; and the

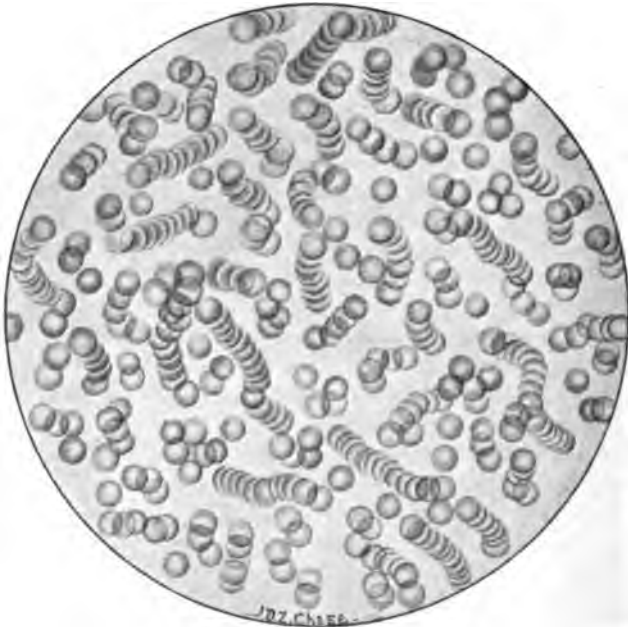


Fig. 170.—Unstained red blood-cells, showing rouleaux formation. (Picture prepared under direction of C. Y. White.)

blood-plaques, or *platelets*. The fluid element of the blood, the *liquor sanguinis*, or *plasma*, is an albuminous and saline liquid of a slightly varying composition. The blood as a whole is red in color, rather viscid,

and alkaline to ordinary indicators, though actually neutral in reaction. The total quantity is about one-thirteenth of the body-weight.

The **erythrocytes**, or **red corpuscles**, are biconcave disks averaging $7\ \mu$ in diameter and having a yellowish or amber color. They are quite uniform in size and regularly rounded. Histologically they are composed essentially of an albuminous substance containing hemoglobin embedded in a delicate stroma. The hemoglobin is the important element, and constitutes about 95 per cent. by weight of the corpuscles. In early fetal life most of the red corpuscles are nucleated, but the nucleated forms later decrease in number and are comparatively scanty at the time of birth. Within the first few months of postfetal life all of them disappear, and in subsequent years nucleated corpuscles are

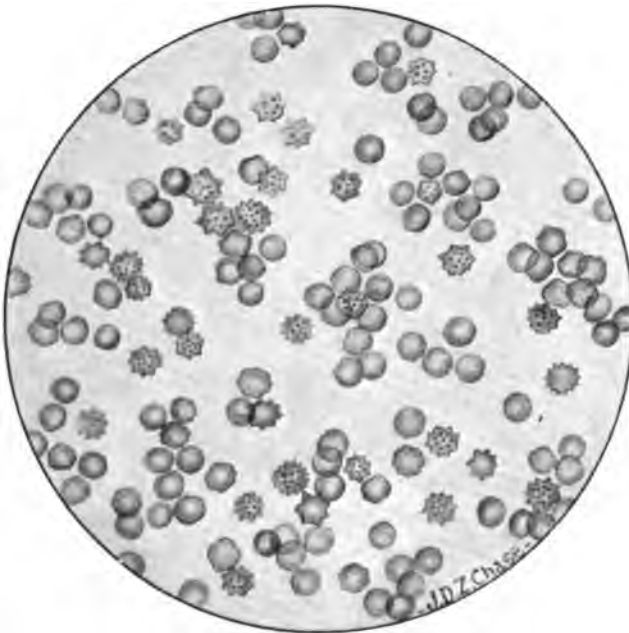


Fig. 171.—Unstained red blood-cells, showing crenation and similarity to sporulating malarial plasmodia. (Picture prepared under direction of C. Y. White.)

present only in cases of disease. According to some recent investigations it would appear that the red cells of adult human blood always contain nuclei demonstrable only by certain staining methods. The supposed nuclei shown in some of these methods are certainly artefacts. As to others, further investigation is needed.

There are about 5,000,000 red corpuscles in the cubic millimeter of the blood of normal individuals. The figures vary slightly at different times in the same individual, and many influences contribute to the production of more lasting changes in number (see pp. 420, 431). The volume of the red corpuscles in a given bulk of blood is dependent upon their number and their size. Observers have reached varying results in

studying the volume, but it may be placed at between 40 and 50 per cent. of the total bulk of the blood.

Skeined Cells.—The method of *vital staining* that has been recently introduced discloses certain varieties of erythrocytes that have excited discussion. A drop of blood is mixed with oxalated sodium chlorid solution, to which brilliant cresyl-blue has been added. The sedimented red corpuscles are then placed under a cover-glass and examined. A certain proportion of the erythrocytes are found to present a skeined or reticulated appearance, which is due to the presence of granules connected by fine threads or a variously arranged network of threads or granules stained by the coloring-matter used. These cells have been regarded by some as degenerative forms, but are more probably young cells. In various anemias in which active hemogenesis is going on the skein cells are more abundant than in normal blood.

The **leukocytes**, or **white corpuscles**, are rounded or spherical bodies presenting a more or less granular appearance in the fresh state. They vary in size from the diameter of the red corpuscles to several times the size of the latter. There are several more or less distinct varieties of leukocytes, but as transitional forms occur classification is

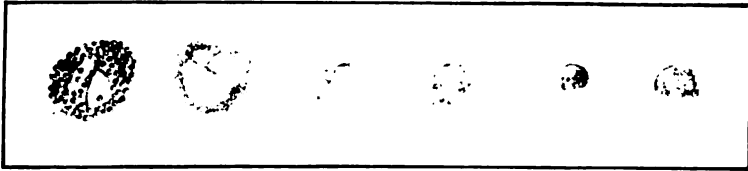


Fig. 172.—Unstained leukocytes.

difficult (Fig. 172). The terminology introduced by Ehrlich is still in quite general use, though recent authorities have disputed many of his views regarding the relationship and source of different forms. Reference will be made to these points in the discussion of the origin of leukocytes.

Ehrlich distinguished the following forms in normal blood: (1) Lymphocytes; (2) large mononuclear; (3) transitional; (4) polymorphonuclear, and (5) eosinophiles. A sixth form, basophiles, may be added, though they occur in only very small numbers in normal blood, and when in larger proportions signify pathological conditions (Fig. 173).

1. **Lymphocytes.**—These are, on the average, about the size of red corpuscles, some a little larger, others smaller; they are spherical in shape and contain a relatively larger round nucleus surrounded by a narrow band of protoplasm often so slight that it is scarcely visible. The nucleus is rich in chromatin, staining deeply with basic stains, and containing one or two nucleoli. Occasionally it is oval or slightly indented on one side. The protoplasm is slightly basophile and with Giemsa or Leishman's stain may present somewhat sparse, fine or coarse granules (azur granulation). The lymphocytes constitute 20 to 25 per cent. of the normal leukocytes.

2. Large Mononuclear Leukocytes.—These are called by some “large lymphocytes,” and, undoubtedly, with certain stains a distinction between the larger forms of lymphocytes and certain large mononuclear forms is impossible. The size varies from 15 to 25 μ ; the cell is ovoid and contains a rather large (7 to 10 μ) round nucleus which is relatively poor in chromatin, so that in the stained blood it is much paler than that of the lymphocyte. There is no nucleolus. The protoplasm is feebly basophile, with only occasional granulation (azur granules). The clear non-granular character of the protoplasm has suggested the term “hyaline cell.”

3. Transitional Leukocytes.—These are similar to the last, but differ in that the nucleus is indented or somewhat irregular in outline. It is very often impossible to determine satisfactorily whether a certain cell is a large mononuclear or a transitional form, and the two may be

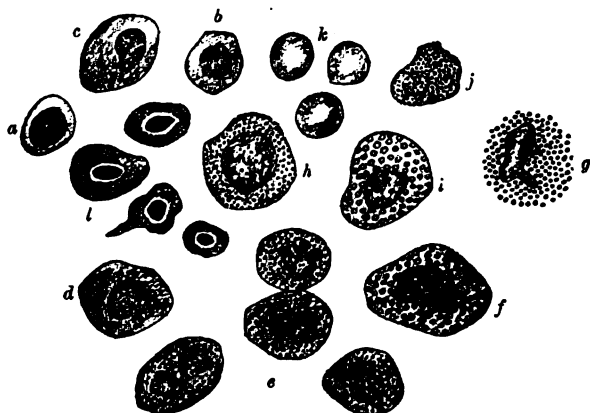


Fig. 173.—Various forms of blood-corpuscles: *a*, Lymphocyte; *b*, lymphocyte approaching *c*; *c*, large mononuclear; *d*, transitional; *e*, polymorphonuclear neutrophile; *f*, polymorphonuclear eosinophile; *g*, broken eosinophile; *h*, neutrophilic myelocyte; *i*, eosinophilous myelocyte; *j*, basophile mast-cell; *k*, red corpuscles; *l*, nucleated red corpuscles.

considered as practically the same. The protoplasm may be free of granules, or may present fine neutrophilic granulation. The large mononuclear and transitional forms together make up 4 to 8 per cent. of the normal leukocytes.

4. Polymorphonuclear Leukocytes; Polynuclear Leukocytes; Neutrophiles.—These are the most numerous forms. They are somewhat smaller than the large mononuclear elements, being from 10 to 12 μ in diameter, and are distinguished by a polymorphous nucleus which is richer in chromatin than that of the large mononuclear form, though less rich than that of the lymphocyte. The nuclei are elongated and variously curved or distorted, so as to resemble the letters S, U, V, Z, etc., and in some cases they are wreath shaped. Frequently, parts of the nucleus are so thin that they are scarcely visible, or actually become broken, and the term “polynuclear” was, therefore, applied. This name is, however, less accurate than the term “polymorphonu-

clear." The amount of chromatin in the nucleus varies greatly, and the size of the nucleus is correspondingly variable. The protoplasm usually contains fine granules, which are closely set and almost completely fill the cell. These granules have a strong affinity for neutral mixtures of anilin or other stains, especially for the triacid stain, and have, therefore, been called the neutrophilic granules (see p. 418). The polymorphonuclear neutrophiles constitute 60 to 70 per cent. of the normal leukocytes.

5. **Eosinophiles.**—These are slightly larger than the polymorphonuclear neutrophiles, their nuclei are polymorphous, though not so much divided and not so basic in staining affinity as the nuclei of the neutrophile. The protoplasm contains large granules which stain intensely with acid stains. In pathological conditions certain other cells containing eosinophile granules are met with (see Myelocytes). They constitute 1 to 4 per cent. of the leukocytes of the normal blood.

6. **Basophiles.**—These are polymorphonuclear cells the nucleus of which stains poorly with basic stains. The protoplasm contains irregular sized granules of intense basic affinity. About 0.5 per cent. of the leukocytes of the normal blood are of this type.

Pathologically, certain other forms of cells of the leukocyte series occur in the blood. Among these are: (a) *Myelocytes*, (b) *plasma cells*, and (c) *leukoblasts*. Occasionally *myeloplaxes*, or marrow giant cells, are present.

(a) **Myelocytes.**—These are large cells identical with the large granular cells of the bone-marrow. They are often three or four times the size of the red corpuscles, and are distinguished by a large, pale, oval nucleus generally placed close to one side of the cell. The protoplasm is sometimes entirely free of granulations, but usually contains fine neutrophile granules. Eosinophile and basophile myelocytes are less frequent, but are sometimes seen in fairly considerable numbers in leukemia. The nucleus is frequently somewhat irregularly outlined, and not rarely suffers degenerative change. Smaller cells, resembling the typical myelocyte in the character of the nucleus and protoplasm, are sometimes observed, and are difficult to classify. Myelocytes occur in exceedingly small numbers, if at all, in normal blood. They are abundant in certain forms of leukemia, and also occur in pernicious anemia and various infectious and systemic diseases.

(b) **Plasma Cells, Stimulation Cells, Irritation Cells (Türk).**—These are oval cells, varying in size from 5 to 15 μ in diameter; and contain an eccentrically placed round or oval nucleus. Both nucleus and cytoplasm are decidedly basophile, especially the latter. There are no true granules, but the deeply stained cytoplasm often presents an indefinite granular appearance. Great variation in the character and staining reactions have been noted by different investigators, and an accurate definition is, therefore, difficult.

(c) **Leukoblasts.**—In various blood diseases, especially in acute leukemia, there are found certain spherical cells varying in size from 8 to 20 μ in diameter, and containing a large, somewhat eccentric nucleus,

poor in chromatin, and a non-granular cytoplasm. These cells have been regarded as large lymphocytes or as non-granular myelocytes, but are now more generally considered as primitive or mother-cells of the leukocyte series, and have, therefore, been named leukoblasts, myeloblasts, primordial cells, etc.

(d) **Myeloplaxes**, or **megakaryocytes**, are large cells, sometimes several times the size of myelocytes, containing a large, highly polymorphous nucleus, and a moderately granular cytoplasm. These cells are occasionally found in the circulating blood in severe anemias.

The **granules** of the leukocytes are classified according to their behavior with the anilin stains. Ehrlich distinguished four important types of granules (Fig. 174).

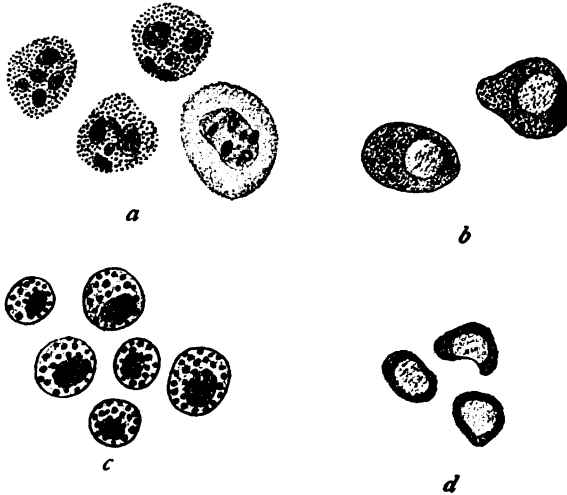


Fig. 174.—Leukocytes, showing various forms of granulation: *a*, Neusser's basophilic perinuclear granules; *b*, large mononuclear cells with δ -granules; *c*, mast-cell granules; *d*, basophilic lymphocytes, δ -granules; the stain in *b*, *c*, and *d* was a mixture of eosin and hematoxylin, the cover-glass being kept in the stain several hours at 37° C. (98.6° F.).

(1) **α -Granules, Eosinophile Granules, or Oxyphile Granules.**—These are coarse granules giving the appearance in the unstained blood of minute fat-droplets; they are highly refractive, and have been shown to be composed of albuminous material. They are distinguished by their strong affinity for acid stains, and in particular for eosin. This circumstance has given rise to the names eosinophile and oxyphile (Fig. 175).

The eosinophile granules in the normal blood occur only in polymorphonuclear leukocytes.

(2) **γ -Granules; Mast-cell Granules.**—These are intensely basophilic, coarse granules, occurring in mononuclear cells. The mast-cell is identical with Waldeyer's plasma-cell of the tissues. It is present in small proportions in the normal blood (Fig. 174).

(3) **δ -granules** are fine basophilic granules occurring in the lymphocytes or large mononuclear cells (Fig. 174).

(4) **ϵ -Granules; Neutrophilic Granules.**—These are the most abundant and the most important of all the forms. They occur as fine granulations, filling up the protoplasm of the polymorphous cells, and they are occasionally present in transitional leukocytes. They are distinguished by their affinity for the neutral mixtures of Ehrlich (Fig. 175). It must be recognized, however, that these granules are, in reality, faintly oxyphilic, receiving the acid stains, such as eosin or acid fuchsin, more readily than basic stains.

In recent years by newer methods (Leishman, Giemsa) a special form of granule, "azur-granules," has been distinguished and has been regarded as highly significant, especially of cells of the lymphocytic series. This view, however, is far from being established. Not improbably immature granules of myeloid cells also present this staining reaction.

Altmann and, later, Schridde and others have described certain fuchsinophile extranuclear granules which are regarded by some as



Fig. 175.—Blood in lienomedullary leukemia, showing several mononuclear neutrophils (myelocytes), one polymorphonuclear neutrophile, and an eosinophile; a nucleated red corpuscle and a lymphocyte are seen in the lower part of the illustration; stained with Ehrlich's triple mixture.

highly characteristic of the lymphocytic series of cells. The significance of these granules is still very uncertain.

The *nature of the granules* of the blood is still obscure. They are undoubtedly connected in some way with the specific function of the leukocytes, but whether they are specific cellular secretions (Ehrlich) or essential anatomical structures (Altmann) is unknown.

The **number of leukocytes** in the normal blood varies considerably. The average number, however, is between 6000 and 8000. Alterations in the number under various circumstances will be discussed later.

Proportions of the Different Forms.—The relative proportions ("differential count") of the different leukocytes are determined by counting large numbers and calculating the percentage proportion of each form. Approximately there are 20 to 30 per cent. lymphocytes, 60 to 70 per cent. polymorphonuclear forms (neutrophils and eosino-

philes), 4 to 8 per cent. transitional and large mononuclear. About 1 to 3 per cent. of all the leukocytes contain eosinophile granules, and occasionally a larger proportion is met with in normal blood. About 0.5 per cent. of the normal leukocytes are basophilic.

Blood-plaques or Platelets.—These are small disks somewhat resembling the red corpuscles, though smaller and without the characteristic biconcavity of the latter. They contain a chromatic body and have been described as nucleated by some observers. They rarely exceed $3\ \mu$ in diameter, and are often much less. They are viscid, and tend to adhere to the other corpuscles or to become agglutinated in clusters. The total number has been estimated at from 150,000 to 500,000 per cubic millimeter. The origin of the platelets is still uncertain. According to some they are derived from the erythrocytes by a process of extrusion from the cytoplasm of the latter; others have held that they are formed by the breaking down of leukocytes. Wright claims to have shown that they are products of the megakaryocytes of the bone-marrow.

The **plasma** of the blood is an albuminous liquid containing mainly serum-albumin and serum-globulin and various saline compounds. The relative proportion of serum-globulin to serum-albumin is as 1 to 1 or $1\frac{1}{2}$. Of the saline constituents, sodium salts are most important, the phosphates, carbonates, sulphates, and chlorids being most abundant. Various other nitrogenous and non-nitrogenous substances are present in small proportions. Reference will be made to some of these below.

BLOOD FORMATION

The process of blood formation is still a matter of uncertainty in some particulars. The prevailing opinion is that all of the blood-corpuscles, erythrocytes and leukocytes, are derived from mesoblastic cells which become differentiated to form the lining endothelia of blood-vessels and lymphatics. From the former group the primitive cells which give rise to erythrocytes and the granular leukocytes take their origin; from the lymphatic endothelia are developed the primitive cells which originate the lymphocytic series. The earliest clearly differentiated blood-cell is a large hemoglobin-containing cell with pale nucleus, found in the mesoblastic columns in which the blood-vessels are differentiated. This is the *primitive erythroblast*. According to older investigators the erythroblasts were derived from this cell. More recent investigations, however, seem to show that this is but a temporary phase in fetal blood formation. Later, the endothelia of the blood-vessels give rise to (1) certain basophilic erythroblasts, containing no hemoglobin, from which the red cells are derived; and (2) myeloblasts from which the myelocytes and their derivatives take their origin. The lymphocytic series, by a similar process of differentiation, is derived from the endothelia of lymphatic channels.

During the earlier portion of fetal life the liver is the principal seat of blood formation; after the third month the spleen and bone-marrow

participate, but the spleen ceases to be active somewhat before the end of fetal life and the liver shortly after birth. The lymphatic glands are the chief source of lymphocytes in intra- and extra-uterine life. It is noteworthy that in many anemic conditions a return to fetal processes of blood formation is observed.

PATHOLOGICAL CHANGES IN THE RED CORPUSCLES

The **size** of the red corpuscles varies in diseases of different kinds. The term *anisocytosis* has been suggested for this irregularity. There may be dwarf corpuscles, 2 to 4 or 5 μ in diameter (*microcytes*); or, on the other hand, giant cells (*megalocytes*), from 9 to 15 μ or even 20 μ in diameter. The small forms frequently have a spherical shape rather than the disk-like form of the normal corpuscle, and may be deeply pigmented. The large corpuscles are often irregular in shape, and are

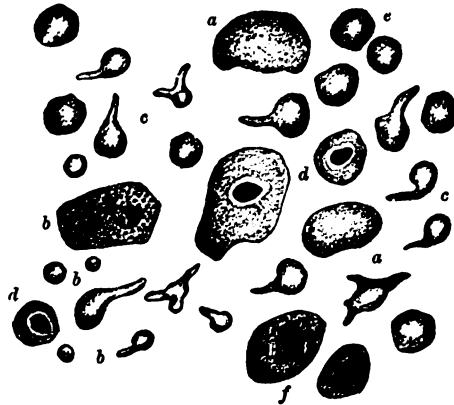


Fig. 176.—Blood from a case of pernicious anemia: *a*, Megalocytes; *b*, microcytes; *c*, poikilocytes; *d*, nucleated erythrocytes; *e*, normal erythrocytes; *f*, leukocytes.

prone to be paler and more basic than normal corpuscles, and usually appear without the concavity of the normal cell (Fig. 176). Some observers have found that the average size of the red corpuscle is greater in certain diseases than in health. This is sometimes the result of hydropic conditions.

The **shape** of the corpuscles often suffers great change, and many forms of irregularity may be observed. The term *poikilocytosis* is applied to this condition (Fig. 176). Some of the poikilocytes may be exceedingly small and may present active movements. These have been termed "pseudobacilli" by Hayem. These changes of form in red corpuscles are regarded by many authorities to be the result of degenerative changes in the protoplasm with consequent ameboid movement which occasions irregular projections. The small forms are doubtless in many cases the result of fragmentation. Ehrlich used the term "schistocyte" to indicate this fact

Dust-corpuscles.—Müller described certain small spherical bodies somewhat resembling the leukocytic granules, but lying free in the plasma and often actively motile. These he termed *hemokonixæ*, or dust-corpuscles. They occur in normal blood as well as in that of various diseases. A number of theories have been offered regarding the nature of these bodies. Some authors regard them as extruded leukocytic granules; others, as portions of protoplasm of the leukocytes. Our own belief is that they are fragments of red corpuscles, similar to those that may be produced by heating fresh blood under a cover-glass to destructive temperatures. Under these circumstances small, bud-like processes are formed on the periphery of the red corpuscles, and some of these may break off and float free in the plasma.

Visible ameboid movements may sometimes be observed under the microscope, especially in severe anemias, such as pernicious anemia.

Nucleated Red Corpuscles, or Erythroblasts.—The red corpuscle when first formed is always nucleated, and throughout fetal life a diminishing proportion of the erythrocytes remains so. At birth and throughout extra-uterine life the erythrocyte is non-nuclear. The loss of the nucleus was formerly attributed to a process of extrusion, but is now believed to be always due to pyknosis, karyorrhexis, and karyolysis within the cell.

Nucleated erythrocytes occur in the severe anemias as in fetal blood. They are more frequent in the severest cases, and in particular in the anemias of children. Some are exceedingly small (*microblasts*), some about the size of the normal red corpuscle (*normoblasts*), and some large and irregular (*megaloblasts*). The stained nucleus of the normoblast is darker and more compact than that of the megaloblast, and is often near the periphery of the cell or apparently partly extruded. The smaller forms appear first and in the more moderate anemias; occasionally they occur in great numbers or crops from time to time (*blood crises*). Degenerations of nucleated red corpuscles may occur, and very frequently are seen in the circulating erythroblast. The usual forms are karyolysis—solution of the chromatin; karyorrhexis—fragmentation of the nucleus; and pyknosis—clumping or condensation of the nuclear structure. Granular degeneration, vacuolation, and nuclear atrophy also occur.

Karyokinetic figures are occasionally seen in the nuclei of erythroblasts, in pernicious anemia, in leukemia, in dibothriocephalus anemia, and in certain anemias of children.

Shadow corpuscles are red corpuscles that have lost their color almost completely and are scarcely visible. They may be observed in severe anemias, and especially in cases of intoxication with blood-poisons.

Ring Bodies.—Cabot, by means of Wright's modification of Leishman's stain, has demonstrated in the red cells of anemic blood the presence of ring bodies, which he is inclined to believe represent the remains of a previously existing nucleus. They were found in 3 cases of pernicious anemia, 3 of lead-poisoning, and 1 of lymphatic leukemia,

in all of which normoblasts were also found. The rings appear to be made up of a series of granules in some cells; in others, of a continuous line. They usually stain red, though blue is not uncommon.

Polychromatophilia.—The normal red corpuscle has a special affinity for acid stains. In diseased conditions it may develop an affinity for basic stains, and when colored with mixtures of acid and basic stains may present tints combining all the stains employed. Thus in staining with eosin and hematoxylin the degenerated corpuscles may present a purplish or violet color, instead of a pink.

Vacuolation and pigmentation of the red corpuscles are rare forms of degeneration. The pigmentation is due to separation of the hemoglobin in the form of irregular granules.

Basic degeneration is a form of degeneration in which minute or rather coarse granules that stain with certain basic stains are found in the substance of the red corpuscles. The number of granules in the cell may be small or large; the cell may be otherwise little altered; it may be polychromatophilic. The condition has been found in various diseases, such as leukemia, pernicious anemia, and malaria, but is most frequent in lead-poisoning. Some observers, by using certain special staining methods, claim that the basic granules are nuclear fragments and regard the process as regenerative rather than a degeneration. It is very probable, however, that the granules seen in these studies have not been those now under discussion.

Alterations of Isotonicity.—All forms of cells have certain osmotic relations, in consequence of which they retain their constituent elements in the presence of surrounding liquids of certain osmotic tension. If the osmotic relations vary or the surrounding liquids are altered, the constituents of the cell may be extruded. In the case of blood-corpuscles distilled water rapidly abstracts the hemoglobin and other substances, but saline solutions of certain strengths do not so affect the corpuscle. The exact strength of a certain saline solution may be determined which will preserve the corpuscle, and this is known as the isotonic strength of the corpuscle expressed in percentage terms of the saline used. Degenerated corpuscles more readily yield their constituents, and the isotonic saline solution is, therefore, of higher percentage. In normal blood the isotonicity of the red corpuscle is generally 0.46 to 0.48 per cent. NaCl; that is, solutions of common salt of this strength do not affect the red corpuscles. In certain anemic diseases the isotonic solutions may be from 0.5 to 0.6 per cent., but often; on the contrary, solutions from 0.40 to 0.44 per cent. may be isotonic.

PATHOLOGICAL CHANGES IN THE LEUKOCYTES

Very frequently degenerations of the nuclei of the leukocytes are observed in the form of fragmentations or karyolytic change. Attention has been called (Neusser) to the presence of basophilic granules about the nucleus in certain forms of disease, such as leukemia, gout, and lithemia in its widest sense. These granules are supposed to be sig-

nificant of disintegration of the nuclei in the process of uric-acid formation. Their nature and significance, however, are unsettled. Occasionally vacuolization and fatty degeneration of leukocytes are observed, and sometimes, as in infectious fevers and in suppuration, glycogen may be found in abnormal quantities. In cover-glass preparations the leukocytes are sometimes found broken or fragmented; or fenestrated, basket-like, pale-staining forms are seen. The latter doubtless occur to some extent in the circulating blood and are frequently spoken of as "leukocytic shadows."

Iodophilia.—This term is applied to a condition of the blood in which there are found in the leukocytes or the plasma granules that stain with iodine, like glycogen. The term "glycogenic reaction" was formerly applied, though recently some question has arisen as to the glycogenic nature of the granules in question. The leukocytes involved in this form of granulation are chiefly the polymorphonuclear. Basophilic leukocytes may be affected, but never the eosinophiles. The intracellular material is found in the form of small granules of regular shape and size, which stain a yellowish-red or brown color with iodine. Less commonly the leukocytes may be diffusely stained, the granules being wanting or so small as to be indistinguishable as granules. The extracorporeal granules are found in more advanced cases. They resemble the intracorporeal granules in appearance.

The significance of iodophilia has not been positively determined. The condition is found in association with leukocytosis or less commonly in the absence of leukocytosis, but it bears no quantitative relation to the degree of leukocytosis. It has been found in various forms of toxemia, in grave anemias due to loss of blood or to other causes, in fevers, and in various other conditions.

The blood-film, without previous fixation, is stained with iodine and iodide of potash in a gum-arabic solution.

PATHOLOGICAL CHANGES IN THE PLASMA

Various disorders of the plasma have been studied. These are mainly of a chemical sort, and consist of the presence of abnormal substances or of normal constituents in excessive quantity. Urea is present in large quantities in some cases of nephritis and uremia, and older authorities believed the symptoms of uremia due to the presence of this substance. This view is no longer held. Uric acid occurs in small quantities in health; but in larger quantities in gout, leukemia, in some forms of leukocytosis, and other disorders of the blood. Sugar is found in excessive quantities in diabetes, in cases of high blood-pressure, in thyroid diseases, and, according to some observations, in cases of carcinoma. Levulose and other carbohydrates are rare constituents of the plasma. Fatty acids may be present in leukemia, diabetes, acute yellow atrophy of the liver, and some other diseases. The quantity of sodium in the plasma increases in anemic diseases.

Certain changes occur in the plasma or serum in certain anemic diseases, as a result of which the globulicidal character is increased. The

nature of these changes is obscure. The presence of toxic substances the result of bacterial action is referred to in the discussion of bacteria.

Hypertonicity of the serum is a term indicating that the salinity of the plasma or serum is such that the blood may be somewhat diluted without destruction of the corpuscles. By graduated dilutions the degree of hypertonicity may be estimated, and is found less in certain diseases than in health. (See *Isotonicity of the Red Corpuscles*.)

Hyperinosis and *hypinosis* are terms designating increased and decreased capability for fibrin formation. The former is met with at times in chlorosis, leukemia or other anemic affections, and in certain infectious diseases. The latter is notably present in leukemia, pernicious anemia, and some cases of hemolysis. There has been much theorizing in regard to these conditions, but very little knowledge of practical importance has been acquired.

PLETHORA

This is the name applied by the older writers to a condition in which the total quantity of blood was supposed to be excessive. It is now recognized that plethora is much less frequent and permanent than was formerly believed. Several varieties were described.

Plethora vera was the name given to the condition in which the quantity of the blood was supposed to be increased without change in its quality. Persons supposed to have this condition are described as robust, with high color and vigorous circulation. They are generally individuals living in luxury. The term "full-blooded" is still applied, but it is recognized that the fulness of the superficial vessels is the result of peculiarities of the circulation rather than of increase in the quantity of blood.

Plethora apocoptica is the term given to conditions in which there is local increase in the blood.

Plethora hydremica is a condition in which the total quantity of the blood is increased by dilution. This was regarded as frequent in cases of cachexia, after hemorrhages, etc.

Experimental evidence might be referred to to substantiate the view that plethora in the strict sense does not often occur as a lasting condition. Temporary plethora is produced by the drinking of large quantities of liquid, but the excretory organs soon dispose of this excess.

OLIGEMIA

This is a term indicating reduction in the quantity of blood. This is met with temporarily after hemorrhage, but very soon serous liquid from the tissues enters the blood-vessels and restores the original quantity. At the time of the hemorrhage the quantity may be immediately reduced to a very great degree without causing death. Serious consequences are averted by the activity of the vasomotor system, the blood-vessels accommodating themselves by contraction to the reduced quantity of blood. Subsequently when liquid of the tissues is absorbed into the blood-vessels the latter dilate and their natural volume is soon

restored. The blood, however, becomes hydremic, or watery. Oligemia or quantitative anemia may possibly occur in certain cachectic and anemic diseases, but this has not been proved, and the relative proportion between the mass of blood and the weight of the body is certainly not much disturbed in any case.

HYDREMIA AND ANHYDREMIA

Hydremia, a diluted or watery condition of the blood, may occur from excessive consumption of water, but active excretion of liquid soon restores the blood to its previous condition. Hemorrhage leads to hydremia in the manner above described; and in the chronic anemias there is possibly some dilution of the serum. It has never been shown, however, in any of the many experiments made to determine this point that the plasma in anemias is less rich in solid constituents than normal plasma. The reduction in solid matter in the blood as a whole is due to the diminution in the number of red corpuscles and changes in their composition.

Anhydremia is a condition in which the plasma of the blood is thickened by the loss of watery elements. This may occur in consequence of excessive sweating or excessive discharge of water from the bowels, kidneys, etc. The number of red corpuscles in a given bulk of blood increases. The specific gravity and the solid residue of the blood as a whole increase correspondingly.

LIPEMIA

This is a pathologic condition in which fat occurs free in the blood-plasma. Fat is always present as a normal constituent of blood, and

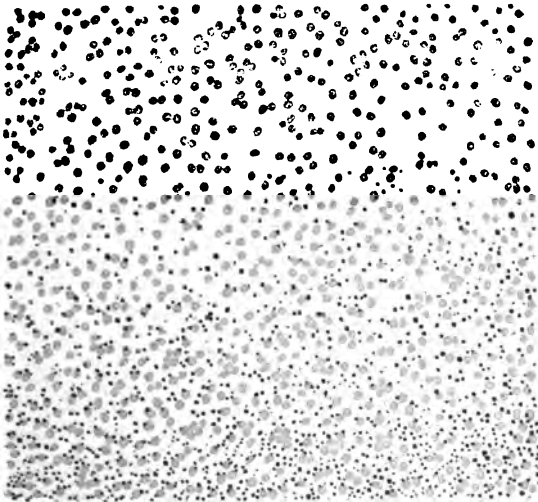


Fig. 177.—Blood from a case of lipemia, stained with osmic acid: upper half of field cleared with oil of turpentine; lower half shows the fat-droplets and granules stained with osmic acid between the blood-corpuscles; enlargement, 100 diameters (after Gumprecht; *Deutsch. med. Woch.*, Sept. 27, 1894).

is in slight excess during the process of digestion. Lipemia occurs in cases of chronic nephritis, diabetes, pulmonary tuberculosis, alcoholism, and some other conditions, and may reach marked grades of severity. The blood may have a milky appearance to the naked eye, and under the microscope highly refractive droplets or granules are observed. The latter stain black with osmic acid (Fig. 177).

The appearance of fat in the blood is ascribed by some to an alteration in its character when being transported and to a decrease in tissue and blood lipase. It may appear in conditions of reduced nutrition when the fat is transferred from fat depots to other situations for metabolic use.

MELANEMIA

This condition is distinguished by the occurrence of dark pigment or granular matter in the circulating blood. It occurs in cases of malaria and certain other fevers. The pigment may be free in the plasma in the form of yellowish or blackish granules; or may be found as small particles in the leukocytes.

HEMOCYTOLYSIS—HEMOGLOBINEMIA

Definition.—Hemocytolysis is the term applied to the conditions in which the red blood-corpuscles are destroyed. The name *hemolysis* is generally employed in the same sense, though it refers to destruction of all of the elements of the blood. In this condition hemoglobin is liberated and is dissolved in the plasma. To this the term "hemoglobinemia" is applicable, but the name "methemoglobinemia" is more appropriate, as the hemoglobin is usually present in the serum in this altered form.

Etiology.—Hemolysis constantly takes place in the liver, the coloring-matter of the blood being converted into bile-pigments. Pathological hemolysis results from the action of various infectious and toxic agents. It occurs in the course of severe malaria, relapsing fever, pneumonia, and various hemorrhagic infections; and is occasioned by many poisons (see Blood-poisons). Excessive cold may be a contributing cause, as seems to be the case in some instances of paroxysmal hemoglobinuria (*q. v.*).

The serum of certain animals has more or less hemolytic effect when injected into other animals. By repeated injections the serum of the animal under experiment may acquire hemolytic properties. Anti-hemolysins have also been produced in experimental investigations and promise to be of practical use, as in the case of certain hemolytic venoms. The explanation of hemolysis elaborated by Ehrlich and later confirmed by Flexner and Noguchi is referred to in the section on Immunity.

Pathological Anatomy.—The blood may present striking morphological changes in the red corpuscles, such as microcytosis, megalocytosis, poikilocytosis, fragmentation, and vacuolation. Shadow cor-

puscles may be abundant, and in the later stages of the process beginning regeneration of the blood causes the presence of nucleated red corpuscles. The blood as a whole is often quite dark in color.

Associated changes are frequently met with in the liver, kidneys, and skin. The hepatic cells are often swollen and more or less degenerated and bile stained. Excessive production of bile (polycholia) may occur. This overproduction, with the swelling of the hepatic cells and the consequent obstruction of the biliary channels, occasions reabsorption of bile and consequent jaundice (so-called "hematogenous jaundice"). The excess of hemoglobin, which cannot be disposed of by the liver, may be excreted in the urine (hemoglobinuria). Sometimes hemoglobin infarcts are met with in the renal tubules; and thrombosis of the renal or other blood-vessels is occasionally observed. Acute nephritis is a rare result.

Pathological Physiology.—Hemocytolysis leads to more or less pronounced disturbance of the internal or tissue respiration, as the altered hemoglobin is incapable of carrying oxygen. Dyspnea and various nervous symptoms are the result. The liberation of cellular constituents (from destruction of the red and white corpuscles) occasions increased coagulability of the blood and the formation of thrombi in arterioles and capillaries. Fever and other general symptoms may be due to the same cause (ferment intoxication).

POLYCYTHEMIA

Polycythemia, or erythrocytosis, is a condition in which the number of red corpuscles in a given bulk of blood is increased. It is met with in a variety of conditions, including certain cardiac diseases with slow failure of compensation, and especially in congenital cyanosis; in carbon-monoxid poisoning and other forms of cyanosis; in residents of high altitudes; in the newborn; and in cases of cholera or other diseases in which liquid discharges cause inspissation of the blood. The explanation of the increased number of corpuscles in some of these conditions has occasioned considerable controversy. It is manifestly possible that erythrocytosis may be *relative* when the number of corpuscles is not actually increased, but their proportion in a given bulk of blood enhanced by diminution in the amount of plasma; or *actual* when there is an increase in the total number of red cells in the body. It does not seem probable that relative erythrocytosis could have more than a brief duration, as in cases of cholera. It is possible, however, that in certain conditions in which the peripheral circulation is stagnant the number of corpuscles in a given bulk of blood drawn from the finger or ear might be relatively increased, without any *actual general* erythrocytosis. The higher count of red corpuscles in the blood of dependent parts or in a finger congested by constriction or cold lends some color to this view. Recent investigators tend toward the opinion that lasting erythrocytosis is an evidence either of stimulation of the bone-marrow, as a result of conditions which interfere with oxidation, or of abnormal

activity of the spleen. The association of marked splenic enlargement in some cases is cited as evidence of the latter view; but convincing proof of the relationship is lacking.

Polycythemia with Chronic Cyanosis and Enlarged Spleen.—A clinical entity comprising these symptoms, together with weakness, prostration, and vertigo, has recently been recognized. No explanation has thus far been given for this condition. In some cases the spleen was found to be tuberculous; in others only chronic hyperplasia was found.

Besides the conditions before referred to as causing cyanosis and polycythemia, certain pulmonary diseases, such as emphysema and chronic poisoning with coal-tar products, such as acetanilid and antipyrin, must be recalled. In some of these cases the spleen may be enlarged and the condition may simulate the one just under consideration. In the reported cases of chronic cyanosis with polycythemia, however, these causes of the polycythemia and cyanosis as well as the ones before referred to are wanting.

LEUKOCYTOSIS

The term "leukocytosis" is given to a more or less transient, but exceptionally chronic, increase in the number of leukocytes, under the stimulus of a foreign agent, bacterial or toxic, or of diseases outside the blood-making organs. The terms "polymorphonuclear leukocytosis," "lymphemia," "eosinophilia," and "myelocythemia" are used to designate increase of the polymorphonuclear leukocytes, lymphocytes, eosinophiles, and myeloid elements respectively.

Etiology.—The causes of leukocytosis are varied. An excessive number of leukocytes in comparison with the figures found in adults is generally observed as a normal condition in the newborn, the number of corpuscles remaining in slight excess during the first year of life. "Physiologic leukocytosis" also occurs in many cases of pregnancy; and is quite constant during the period of digestion in healthy persons, protein food being more striking in the effect than a farinaceous or mixed diet. In some diseases of the stomach postdigestive leukocytosis seems not to occur.

Inflammatory and Infectious Leukocytosis.—Among the strictly pathological forms of leukocytosis the most important are those due to inflammations and infections of various kinds. Croupous pneumonia occasions considerable increase of leukocytes in most cases, and this is continuous until the final decline of the fever. Suppurations of all kinds act in a similar manner. Inflammations of the serous membranes—peritonitis, pleurisy, meningitis—may be attended by moderate or severe leukocytosis. Among the acute infectious fevers there are some in which leukocytosis occurs and others in which this is wanting, and this fact often proves valuable to the clinician. Among those in which the leukocytes do not increase in number are typhoid fever, influenza, malaria, and acute miliary tuberculosis.

Cachectic leukocytosis occurs in a variety of marantic conditions, and toward the end of life in any case of wasting disease there may be a great increase in the number of leukocytes. This agonal or terminal leukocytosis is either cachectic (toxic) in nature or it may be due to terminal infections.

Malignant tumors frequently cause leukocytosis.

Hemorrhage may occasion increase in the number of white corpuscles, more or less proportioned to the quantity of blood lost.

Mechanical and Thermal Causes.—Massage and cold baths frequently cause increase in the number of leukocytes for a time.

Medicinal leukocytosis, or that due to the introduction of various drugs, is probably allied to infectious and cachectic leukocytosis in the manner of its production.

Pathogenesis.—The nature of leukocytosis has been the subject of much controversy. The earliest view regarding the pathogenesis of leukocytosis was that in some manner excessive production of leukocytes took place either in the blood or elsewhere. Later some investigators claimed that there was evidence that the leukocytes were not destroyed as rapidly as in health. Still later the presence of chemotactic substances, positive or negative, in the blood was regarded as the cause of increase or decrease of leukocytes. At present it seems correct to interpret leukocytosis as a reaction of the blood-making tissues to agents which stimulate them to overactivity. Such influence is most frequently manifested in the bone-marrow (which occasions the prevalent type of leukocytosis—polymorphonuclear), but sometimes the lymphatic glands are principally affected and lymphemia results.

Dormant myeloid elements in the spleen or elsewhere may be stimulated to activity and may play a considerable part in the development of leukocytosis. This is more likely to be the case in more chronic types.

According to present conceptions, the explanation of leukocytosis on the basis of chemotactic effects of circulating toxic agents, the blood-making organs being only passive participants, must be abandoned.

As a reaction on the part of blood-making tissues is the important feature in the process, it follows that toxic agents too feeble to excite such reaction may fail to produce leukocytosis; and overactive irritants may have a paralyzing effect.

Character of the Blood.—The blood in leukocytosis varies considerably in character. The number of leukocytes may be only moderately increased (10,000 to 20,000) or may be excessive (50,000 to 100,000).

In the majority of cases of leukocytosis the polymorphonuclear elements are in relative as well as actual excess, the mononuclear elements being actually increased in number, but relatively deficient (Fig. 178). The proportion of polymorphonuclear elements is frequently 80 to 85 per cent., and sometimes 90 or 95 per cent., instead of 65 to 70 per cent. In the leukocytoses following hemorrhage, in cachectic leukocytosis, in septic leukocytoses, and that due to malignant tumors the polymorphonuclear cells are usually increased, while in the leukocytosis

of the newborn and in some tumors, especially lymphomata, the mononuclear elements predominate. Lymphemia is occasionally met with in infections in which ordinarily polymorphonuclear leukocytosis would occur. Some unknown factor, perhaps individual, operates in such cases. Lymphemia is also observed in pertussis, syphilis, typhoid fever, and scarlatina. Eosinophilia has been observed in a variety of skin diseases, in animal parasitism, especially trichinosis, in anaphylaxis, asthma, etc. Myelocythemia has been found in various severe infections and in cases of metastasis of tumors to the bone-marrow. It is often pronounced in the so-called *anemia pseudoleukemica infantum*.

Pathological Physiology.—Leukocytosis certainly exercises some profound influence upon the system, but the exact nature of this influence is unsettled. Those who contend in favor of the phagocytic theory of immunity claim, more or less directly, that the increase of leukocytes is a protective process, the purpose being the removal and destruction of irritants. This view seems to have gained ground with increased

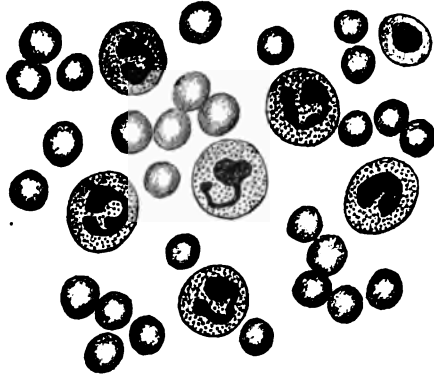


Fig. 178.—Septic leukocytosis, showing marked increase of polymorphonuclear leukocytes.

knowledge of the mechanism of infection. Others believe that leukocytosis is part of the cellular processes concerned in the production of immunizing substances. There is certainly more active destruction of leukocytes in leukocytosis than in health, as is evidenced by the increase of xanthin bases and uric acid in the urine; and it may be that in this destruction protective substances are liberated.

LEUKOPENIA

This is a condition in which there is deficiency in the number of leukocytes. This is met with in moderate degree in various diseases, such as tuberculosis, typhoid fever, some cases of cachexia, inanition, splenomegaly, progressive pernicious anemia, etc. The nature of the condition is not entirely clear. Some have held that it is due to destruction of leukocytes (*leukolysis*), while others claim that it is the result of altered distribution of the leukocytes. It has been shown by experimentors that the injection of certain micro-organisms or toxic sub-

stances may produce, first, a decrease in the number of leukocytes, and then an increase. The primary leukopenia is explained by some as the result of active destruction of leukocytes, but the conditions of the urine do not give evidence of such active destruction, and others have shown that the capillaries of the lungs, liver, and other organs are overfilled with leukocytes during this stage. The assumption, therefore, seemed warranted that leukopenia might result from disturbance in the distribution of the leukocytes.

According to more modern conceptions, however, leukopenia may be regarded as a result of unfavorable action upon the blood-making tissues of toxic agents.

ANEMIA

Definition.—This term includes a variety of conditions in which the blood is reduced in quality in one constituent or another. The term *oligocythemia* indicates a reduction in the number of red corpuscles, while the name *oligochromemia* indicates a reduction in the coloring-matter of the corpuscles. Usually these conditions are associated.

Classification of Anemias.—It is not as yet possible to offer a strictly scientific classification, but for ordinary purposes the old division into *primary* and *secondary anemias* may be retained. The term “primary anemia” may be given to forms in which the anemia is the striking pathological condition. The older writers used the name to indicate that the anemia was an essential disease of the blood itself and dependent upon no preceding affection, excepting possibly a disturbance of the hematopoietic organs. The term “secondary anemia,” or “symptomatic anemia,” may be used to designate anemic conditions in which some underlying disease that has occasioned the anemia is conspicuous. According to the classification here offered, all anemias are recognized as secondary in the strict sense, but those in which the underlying disease is not conspicuous are classified as primary, and those in which the original disease is conspicuous as secondary. Another aspect of the matter, within the terms of the definition, is that in the diseases classified as primary, the effects of the original condition, whether toxemia, infection, or of other sort, are manifested most strikingly in the blood-making apparatus. In the secondary anemias such effects are subsidiary in importance and relatively inconspicuous.

THE SECONDARY ANEMIAS

Etiology.—Various *unsanitary conditions* may influence the character of the blood by the constant disturbance of the organic functions. A cause of immediate anemia is *hemorrhage*. This first leads to reduction in the quantity of blood; and later by absorption of liquid from the tissues to dilution of the blood, or *hydremia*. Finally, after a variable period, the character of the blood is restored by regeneration of corpuscles and of coloring-matter. *Parasites* of various sorts may lead to anemia. Among the more important are the intestinal worms,

Uncinaria duodenalis, *Dibothriocephalus latus*, and *Anguillula intestinalis*. The mode of action of these is not entirely clear. Some have held that they cause anemia by loss of blood through the intestine, and this is probably true in the case of *Anguillula* and *Uncinaria*, but marked anemia may occur from the presence of *Bothriocephalus*, which is not a blood-sucker and does not occasion hemorrhage. An explanation worthy of consideration in these cases is that the parasites generate poisons either in their ordinary life or by their death and decomposition, and that these poisons are the cause of the anemia. Recent investigations seem to indicate that certain lipoids are the direct hemolytic cause of the anemia in cases of *bothriocephalus* invasion. Other intestinal parasites may occasion more or less anemia directly or indirectly. The parasites occurring in the blood itself, notably the malarial organism, may cause extreme anemia. *Infectious diseases*, especially streptococcus infections, frequently lead to impoverishment of the blood. In the acute febrile diseases, such as typhoid fever, rheumatism, and pneumonia, the anemia may not be conspicuous during the progress of the disease, but becomes apparent after the fever has subsided. This may be explained by the assumption that increased respiration and sweating cause inspissation of the blood and relative increase in the number of red corpuscles during the existence of fever, so that the anemia is unnoticed. In chronic infections, such as syphilis and tuberculosis, marked anemia may occur. Among the *poisons* capable of producing anemia are lead, arsenic, phosphorus, and other metallic substances, and experimentally pyrogallol, nitrobenzol, pyrocin, and various coal-tar products have been used to produce anemia. The anemias of various infectious diseases are undoubtedly toxic in character, and very probably those occurring in gastro-intestinal and nutritional diseases are similarly the result of the action of poisons generated within the body. *Organic diseases* and *new growths* of various sorts may occasion anemia by the general disturbance of health, by toxic products generated in the course of disease, or by hemorrhage.

Pathological Anatomy.—The condition of the blood in secondary anemias varies with the duration and grade of the anemia. In moderate cases the number of red corpuscles decreases slightly (4,000,000 to 3,000,000), and the hemoglobin is correspondingly reduced, though usually somewhat more strikingly than the corpuscles. The fresh blood may show no visible changes under the microscope, and even in stained preparations the appearance may be normal. More marked anemia is distinguished by greater reduction, the number of corpuscles sinking to 2,500,000 or 2,000,000 per cubic millimeter in extreme cases. Examination of the fresh blood shows pallor of the corpuscles and various irregularities in size (microcytes and megalocytes) and shape (poikilocytes). Nucleated red corpuscles may be present in small numbers, normoblasts predominating. The stained blood may disclose degeneration of the corpuscles by the presence of polychromatophilic forms. The leukocytes do not play an essential part in this form of anemia. Their number may be normal or reduced; in other cases leukocytosis is present.

The relative proportions of the different forms is usually about normal. Myelocytes are occasionally present.

Associated changes in various organs may be met with. Among these are parenchymatous and fatty degeneration of the heart, kidneys, and liver. These conditions have often been ascribed to reduced oxidation, which was supposed to be due to poverty in hemoglobin. Physiological studies, however, do not establish the existence of a reduction in the respiratory exchange of gases. It is likely that toxic conditions of the blood occur in anemia, and that the poisons act directly upon the affected organs.

Pathological Physiology.—The process of oxidation is of particular interest in anemia, and, as has been stated, recent investigations show that the consumption of oxygen and elimination of carbon dioxide are normal. To accomplish this result more active circulation and greater energy of the tissues are required. Partly in consequence of the latter, diseases of the organs named in the last paragraph result; and at the same time some of the characteristic symptoms (palpitations, dyspnea) are produced. In severe secondary anemias increased tissue-waste occurs, and nitrogen is discharged in excess of that digested.

THE PRIMARY ANEMIAS

The principal conditions included under this title are chlorosis, progressive pernicious anemia, leukemia, and Hodgkin's disease. The modern tendency is to discuss the last two apart from anemias; but not only established custom, but the involvement of blood-making organs and the occurrence of actual anemia in these diseases justify the classification adhered to. The term *simple primary anemia* is sometimes used to designate a form of anemia without distinct cause, and characterized by moderate oligocythemia. There are, it is true, occasional cases of moderate anemia in which no definite precedent disease can be discovered; but these are exceptional cases, and are to be considered as secondary anemias in which the underlying disease is latent. Cases of this sort do not conform to a definite type, and cannot, therefore, be considered as illustrating a special form of anemia. Another term frequently used is *splenic anemia*. This is even less satisfactorily defined. Splenic enlargement may occur in any of the primary anemias, and may in some cases be excessive. Moreover, some of the distinctly secondary anemias (as those of rickets, syphilis, and malaria) are very often attended with splenic enlargement. There is a group of conditions properly included under the title *splenomegaly* in which more or less anemia may occur, but this title rather than splenic anemia is preferable.

CHLOROSIS

Definition.—Chlorosis is a primary anemia due to retarded hemogenesis, characterized by a peculiar pallor and marked reduction in the percentage of hemoglobin, and occurring almost exclusively in young girls and women.

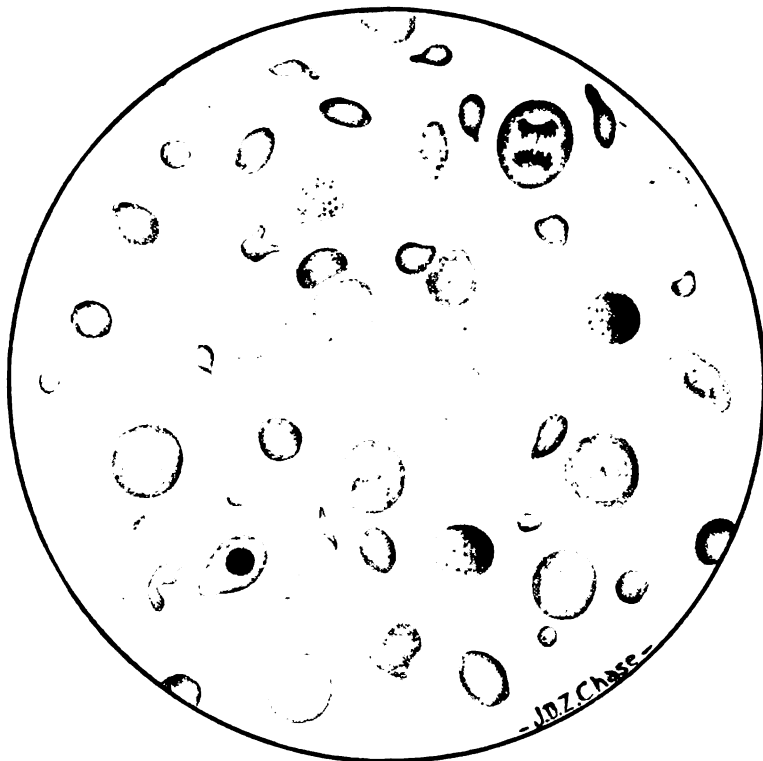
Etiology.—Chlorosis is most frequent at the time of beginning menstruation and during the years immediately following this. A form of *late chlorosis* has been described in women above thirty years of age and at the menopause; but the nature of this is doubtful. *Chlorosis in the male* is still more doubtful, though a few cases have been described by competent observers. Hereditary tendencies are of etiological importance. The disease occurs more frequently in families in which tuberculosis is common than in those not so affected. Constitutional predisposition is also an important factor, poorly developed girls, and particularly those of delicate mould, being especially liable to the disease. Virchow found hypoplasia of the heart and great vessels, and Rokitansky the same condition in the generative organs, and pathologists have been inclined to regard these as important factors in the development of the disease.

Various exciting causes have been considered as of more or less importance. Emotional excitement was regarded as a prime cause by ancient authorities, and in consequence such terms as *icterus seu febris amantium* were applied. Home-sickness, grief, etc., are causes of moment. Intestinal auto-intoxication has been regarded as the essential factor by many, but physiological chemists fail to find evidences of the existence of such intoxication. Menstrual disturbances are important as symptoms, and have often been regarded as causes. The hypoplasia of the genital organs adds some probability to this view, but more definite evidence is wanting. Von Noorden strongly advocates a theory that chlorosis is due to a failure of some internal secretion of the ovaries.

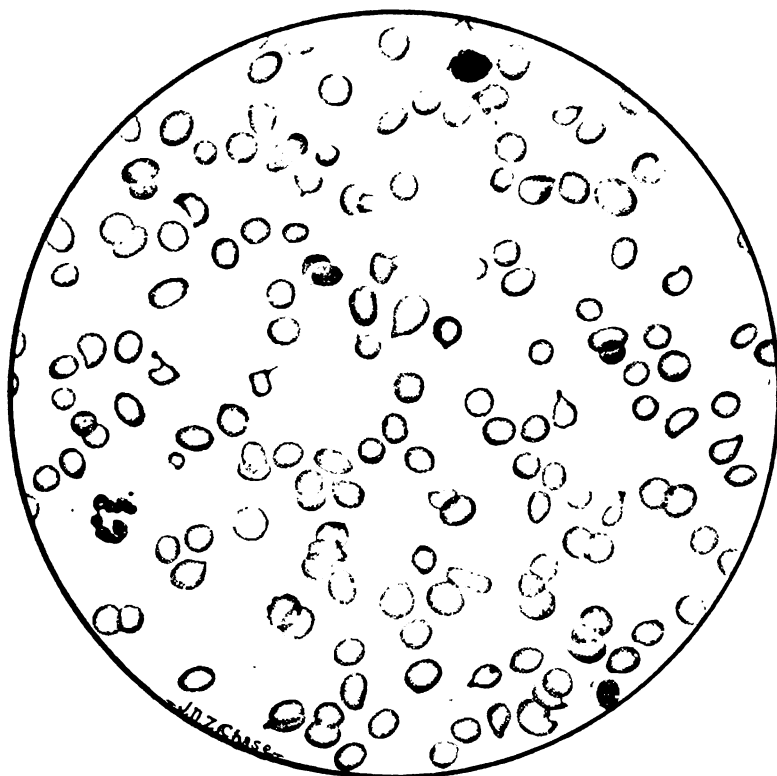
At the present time it seems most likely that chlorosis is due to faulty development, and especially to a want of proper hemogenetic power.

Pathological Anatomy.—The hypoplasia of the vascular and generative systems has been referred to. These are primary lesions, and possibly causal. Various secondary diseases may be encountered, as in other anemias. Among these, myocardiac degeneration and dilatation are most important, though they do not attain high grades of severity. The spleen is frequently a little enlarged. Peculiar yellowish or greenish pigmentation of the skin is a striking feature. The pigment is doubtless altered hemoglobin, but its exact nature is unknown.

The blood is paler than normal and watery. The specific gravity decreases progressively, and the solid matter is deficient. Increased coagulability is sometimes observed. The number of red corpuscles may be normal, even in well-developed cases, but the proportion of hemoglobin sinks progressively. In prolonged cases the corpuscles become reduced in number, but the deficiency of hemoglobin continues to be excessive. Severe cases of chlorosis frequently show 3,000,000 or 2,000,000 red corpuscles per cubic millimeter and 30 to 20 per cent. of hemoglobin. The red corpuscles may be little altered in appearance in the early stages; later, great pallor of the cells, and irregularities in size and shape are frequent, nucleated red corpuscles (especially normo-



Pernicious anemia. (Drawing made under the direction of Dr. C. Y. White.)



Chlorosis. (Drawing made under the direction of Dr. C. Y. White.)

blasts) make their appearance. The latter sometimes occur in great numbers in crops (blood crises). The leukocytes are usually normal in number and kind; but in some cases myelocytes have been met with.

During the process of recovery from chlorosis the red corpuscles increase in number before any change occurs in the percentage of hemoglobin.

Pathological Physiology.—Chlorosis resembles the secondary anemias in most particulars, as far as its influence on the general health is concerned. Some of the symptoms (cardiac and menstrual) are doubtless due to primary abnormalities of structure. The preservation of the subcutaneous fat despite advancing anemia is a striking feature. It is explained by von Noorden on the assumption that the quiet and warmth which chlorotics find necessary to their comfort lead to accumulation of fat. Decreased oxidation is certainly not the cause.

PROGRESSIVE PERNICIOUS ANEMIA

Definition.—Progressive pernicious anemia is a form of hemolytic anemia characterized by certain hematologic features significant of pathological activity of the bone-marrow. It is probably always fatal, though a few instances of recovery have been reported by competent authorities. An exact definition and a positive clinical differentiation from certain other conditions are not possible.

Etiology and Pathogenesis.—The disease was first described by Addison as a wholly causeless anemia, that is, an anemia independent of preceding disease of any sort. Subsequent investigation seemed to show that it might be secondary to other diseases. Thus intense anemias were found during pregnancy and lactation, in certain gastro-intestinal affections, including atrophy of the gastric and intestinal mucosa, ulcerations and carcinoma, and in cases of intestinal parasitism (uncinaria, bothriocephalus). A rigid scrutiny of such cases discloses the fact that these are usually instances of intense secondary anemia, though the resemblance to true pernicious anemia may be puzzlingly close. In the cases in which true pernicious anemia must be admitted the relation may be merely a coincidence. Considerable evidence has, however, accumulated to show that gastro-intestinal infections and toxemias may be the underlying cause of the disease. First, it was shown that pernicious anemia is essentially a hemolytic anemia from the facts that the blood-picture is in many respects that of direct experimental hemolytic anemias, that the pigmentation of the liver and spleen indicate hemolysis, and the urine and feces give evidence of excessive liberation of blood-pigment. Second, it was noted that the distribution of pigment in the liver and spleen strongly suggested hemolysis in the area of the portal circulation; and third, the frequent association of oral infection (glossitis, ulcers in the mouth, on the gums, etc.) or gastro-intestinal disease further strengthened this view. The discovery of hemolytic substances in the bodies of bothriocephalus taken

in conjunction with the anemia occasioned by this parasite was another factor in the evidence.

There is some ground for believing that some sort of primary vulnerability of the bone-marrow may be of importance; but it is much more probable that the marrow is affected by toxic agents derived from outside sources than that there is a primary disease of the marrow.

Among clinical causes: *age* (usually after adult years have been reached); *sex* (more often females); *nervous shocks*, *privation*, and *insanitary surroundings* have been noted. *Malaria*, *syphilis*, *tuberculosis*, and other infections, as well as repeated *hemorrhages*, have been regarded as causes. In connection with all of these it must be remembered that the differentiation of intense secondary anemia from pernicious anemia is often very difficult.

Pathological Anatomy.—Various secondary changes are met with, those in the blood-making organs being most important. The bone-marrow of the long bones is red and softened and often quite hemorrhagic (for details, see Bone-marrow). This change was formerly regarded as a primary and causal one. At the present time it is looked upon as secondary and reactive to a toxemia and, in part, to the hemolytic anemia itself. In part, at least, it represents the effort of the bone-marrow to compensate for the active blood destruction. The spleen is sometimes enlarged, and may be considerably so. (Pigmentation of the spleen will be referred to below.)

The liver, kidneys, and especially the heart suffer degenerative changes (fatty) in severe cases. Similar alterations in the blood-vessels may cause punctate hemorrhages (especially in the retina), or larger hemorrhages in various situations. The lesions of the gastro-intestinal tract have been referred to. Some of them are doubtless secondary to the anemia; others may be primary.

Degenerations of the posterior and lateral columns of the spinal cord are frequent. They seem to be due to a toxic agent rather than to hemorrhages.

Pigmentation of the liver, spleen, kidneys, and other organs is a significant condition in evidence of the active hemolysis supposed to occur in this disease. The pigmentation of the liver is most important, and seems to be characteristic. It occurs in the hepatic cells at the periphery of the lobules and in the endothelial cells of the lymphatic channels and capillaries in the same situation. The pigment is iron-containing, and may be well demonstrated by applying the iron reactions (sulphid of ammonium; hydrochloric acid and ferrocyanid of potassium—forming Prussian blue).

The Blood.—The color of the blood is often strikingly pale; though it may be dark in spite of marked anemia. In some strikingly hemolytic cases the blood-plasma may be deeply tinged with hemoglobin or with bile-pigment. The specific gravity is reduced. The marked features of the disease are pronounced oligocythemia, marked changes in the character of the red cells, and a color-index somewhat above normal, which contrasts with the low color-index of severe secondary anemias.

The oligocythemia progresses rapidly, and in ordinary cases the number of red corpuscles sinks to 1,000,000 or less per cubic millimeter; at the same time changes in size (microcytes and megalocytes) and in shape (poikilocytes) make their appearance, and reach grades rarely attained in other diseases (Fig. 179). An important feature is the number of macrocytes. A general survey of the microscopical field at once indicates that the average size of the corpuscles is evidently increased. Nucleated red corpuscles are always present in some numbers and are usually abundant (Fig. 179). The larger and polychromatophilic forms (megaloblasts), as a rule, predominate; but in some cases the smaller forms are more abundant. Karyokinetic figures may be found in the nuclei. Polychromatophilia and basic granulation are generally pronounced. The leukocytes may be decreased or normal in number; in the late stages leukocytosis is not uncommon, and it may become quite



Fig. 179.—Blood in pernicious anemia, showing irregularity in the size and shape of the red corpuscles; one nucleated red corpuscle (megaloblast) and two lymphocytes; stained with Ehrlich's triple mixture.

marked. The larger mononuclear leukocytes are usually more abundant than in health, and myelocytes often occur in considerable numbers. In the terminal leukocytosis of pernicious anemia the lymphocytes often predominate.

APLASTIC ANEMIA

Occasional cases of severe anemia running a rapid course to a fatal termination have been reported, in which the bone-marrow has shown a high grade of hypoplasia or even total aplasia. In these cases the blood gives evidence (marked reduction in the number of red cells, low color-index, great reduction of the proportion of polymorphonuclear cells, relative and actual increase of lymphocytes, absence of myelocytes and very few nucleated red cells) of the inactivity or aplasia of the marrow. These cases seem classifiable as types of progressive pernicious anemia in which the response of the bone-marrow to the demand for hemogenesis is nearly or quite wanting. Possibly the toxic agent may be directly destructive to the bone-marrow, as it is to the blood.

The bone-marrow is yellow or white, and on microscopical section the specific marrow cells may be wholly wanting.

HEMOLYTIC ICTERO-ANEMIA

In recent years several clinical types of hemolytic anemia with jaundice have been described. These may properly be discussed here because of the close relationship in pathogenesis and the difficulty in fully differentiating some of these conditions, either clinically or pathologically, from genuine pernicious anemia. The evidences of hemolysis are more striking in these diseases, while the indications of bone-marrow reaction are less marked, but border-line cases merge gradually into the picture of pernicious anemia.

A congenital and an acquired form of hemolytic ictero-anemia have been described. In each there is more or less pronounced anemia, jaundice, and splenic enlargement. The congenital form often affects several members of a family, is comparatively mild, and may continue for years without grave disturbance of health. Splenic enlargement is marked. In the acquired form the anemia and jaundice are more marked and splenic enlargement usually less so. The prognosis is more grave. In both, the evidences of hemolysis (jaundice, without acholic stools, urobilinuria, hemorrhagic tendencies) are pronounced. The red corpuscles show decided fragility, being hemolyzed in much more concentrated salt solutions than are normal red corpuscles.

LEUKEMIA

Definition.—Leukemia is a hyperplastic disease of the hemogenic organs accompanied by increase in the number of leukocytes in the circulating blood, and by the presence also of cell types not found normally outside the blood-making tissues.

Etiology.—The actual cause of leukemia, as well as the essential nature of the disease, remain obscure. Various diseases (malaria, syphilis, rickets, etc.) have been regarded as predisposing causes. The same is true of pregnancy, lactation, traumatism, exposure, and other influences. To some, heredity has seemed to be an important element.

Infection has been suspected as the direct cause of leukemia by many observers, and various forms of bacteria have been discovered in the blood and tissues. There are certainly some very striking facts in favor of an infectious nature, the most important being the apparent contagiousness in a few cases. The various micro-organisms need not be enumerated, as none of them has been proved to be pathogenic. Bodies resembling protozoa have been found in the blood and in the organs (lymphatic glands), but the nature and significance of these are uncertain.

Pathological Anatomy.—It is impossible to classify leukemia with certainty, but the evidence at present seems to justify the belief that it is closely related to neoplastic processes. Reference to this aspect of the matter will be found in the sections on Lymphatic Glands and Bone-marrow.

In a certain sense the lesions of leukemia might be classed as hyper-

trophy or hyperplasia of the hemogenic tissues; but there is evidence of a progressive process that goes beyond the limits of ordinary hypertrophies. Enlargement of the spleen or of the lymphatic glands is the conspicuous pathological feature. The secondary lesions in organs that have ceased to be active hemogenic structures (spleen, liver, and perivascular tissues elsewhere) appear to be metaplastic, in the sense that the endothelia may reassume a latent capacity and as in fetal life initiate new series of blood-making cells. This process rather than metastasis or mere deposition accounts for the foci of myeloid or lymphadenoid tissue found in practically all parts of the body. Two types of leukemia may be distinguished: the myeloid or myeloic and the lymphatic. The former originates in the bone-marrow, and is characterized by hyperplasia of the myelocytic series of cells. Not only myelocytes, but their predecessors, myeloblasts and various intermediary stages representing undeveloped myelocytes, may make up the bulk of the tissue. The erythroblastic cells are crowded out, though not invariably, and exceptionally may be conspicuous. In certain cases, especially in very acute forms, myeloblastic cells difficult to distinguish from cells of the lymphocytic series may be conspicuous both in the lesions of the bone-marrow and other organs and in the blood. Many if not most of the cases of so-called acute lymphatic leukemia belong in this group. Lymphatic leukemia originates in the lymphatic glands or other lymphadenoid tissues, and consists essentially in an active proliferation of lymphocytes. The bone-marrow, spleen, and other organs may be secondarily involved. The contention that all forms of leukemia originate in the bone-marrow, which was at one time commonly believed, was largely based upon the discovery that sometimes in so-called acute lymphatic leukemia the bone-marrow was found affected and not the lymphatic glands. In the light of present knowledge these cases were probably instances of myeloblastic leukemia.

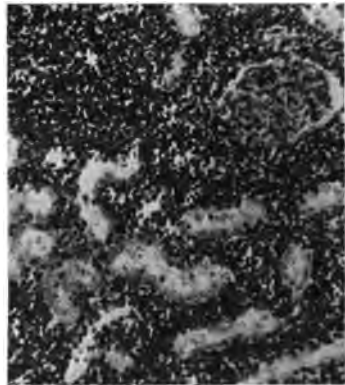


Fig. 180.—Lymphoid infiltrations between the renal tubules, from a case of leukemia.

Occasionally the primary disease is in the lymphadenoid tissues of the gastro-intestinal tract. Primary dermal leukemia has been described (lymphoderma pernicioso), but is not satisfactorily established.

Among the secondary lesions of leukemia are invasions of the liver, kidneys, lungs, heart, and other tissues. The organs show areas of light color, or a streaked or mottled appearance, due to masses of myelocytic or lymphoid cells (Fig. 180). Secondary degenerations of the heart, liver, and kidneys may result from the deposits, or from the impoverished state of the blood and the presence of toxic substances. Scleroses of the spinal cord may be met with, as in pernicious anemia.

The blood is often light in color and may be quite milky in appearance. The specific gravity is lowered. Coagulation is slow; this has been attributed to the presence of albumoses in the blood.

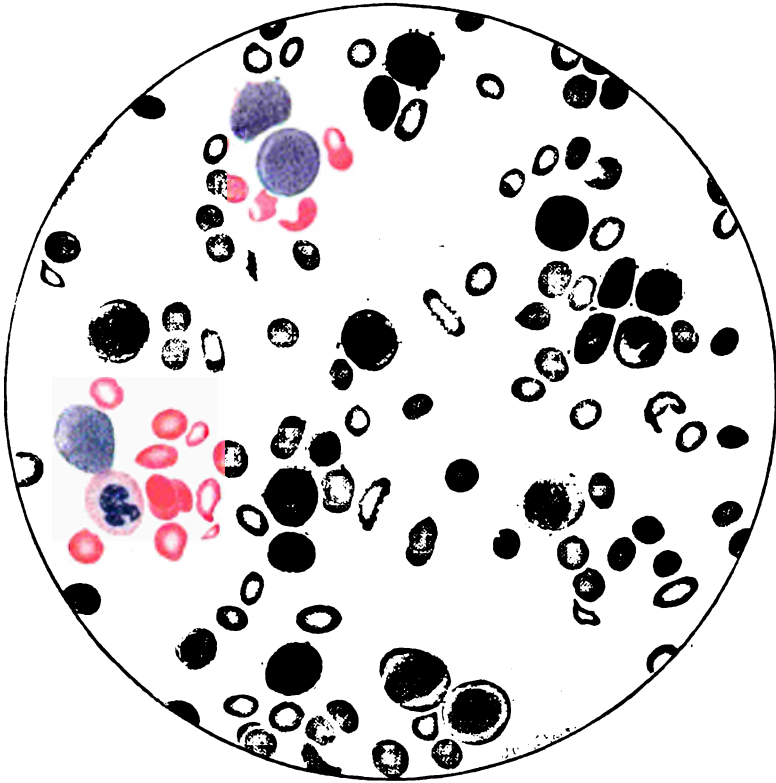
The conspicuous feature in the blood is the increased number of leukocytes. In moderate cases there are from 100,000 to 300,000 white corpuscles per cubic millimeter. In severe cases the number is much greater; while in mild or beginning cases, or in cases under active treatment, the number may for a time be normal or subnormal. Rapid fluctuations in number are very common.

Leukemia is usually a chronic disease. The blood-picture indicates the type of the lesions, and we may thus recognize a myeloid or lymphatic form.

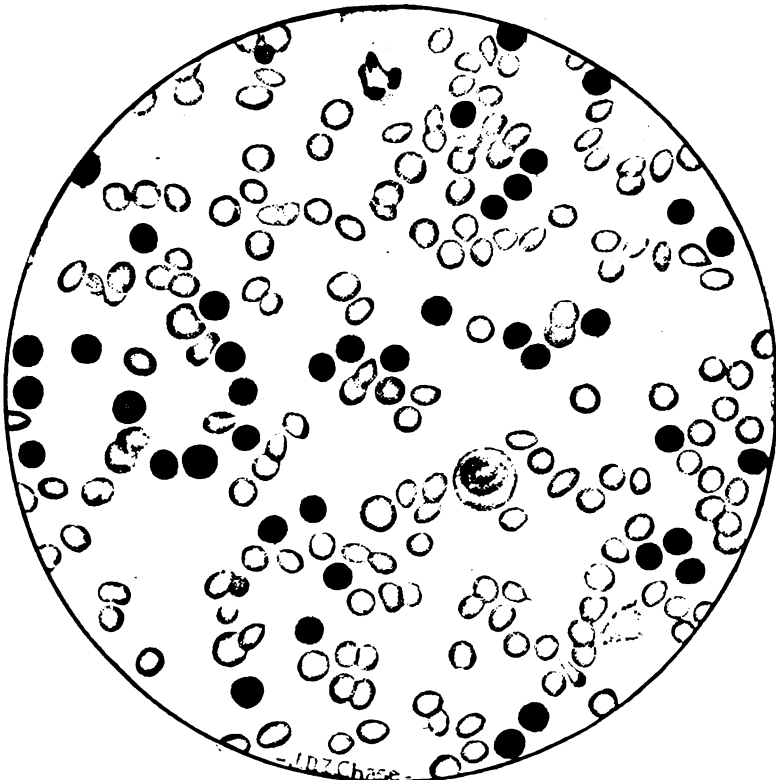
Myeloid Type.—Enlargement of the spleen is the conspicuous clinical feature. The blood presents a great excess of white corpuscles and more or less decided poverty in red cells. The proportion of white to red corpuscles is often 1 : 3, 1 : 2, or even 1 : 1. The larger mononuclear leukocytes (including normal mononuclear and transitional elements and myelocytes) predominate over the lymphocytes and polymorphonuclear elements (see Fig. 175). The latter two forms, however, are actually increased. Myelocytes are usually found in great numbers, and evidence the myeloid nature of the disease. Not only the typical neutrophilic myelocyte, but more or less abundant eosinophilic and basophilic forms and some without granules or with a mixture of basophile and neutrophile granules may be found. Cells corresponding to the myeloblasts may also be found, sometimes abundantly, especially in acute cases. There is usually an actual increase in the number of eosinophile elements, but the percentage proportion is rarely increased. Basophilic leukocytes (mast-cells) are present in numbers greatly in excess of those found in health. Karyokinetic leukocytes are found in small numbers. The red corpuscles present the usual features of anemic blood, and nucleated forms, especially normoblasts, may be abundant. The blood-picture is an extremely variegated one, and the predominance of large cells is the feature that stands out most prominently.

A peculiar constituent of the blood are the Charcot-Neumann crystals. These are polyhedral, needle-shaped crystals of uncertain composition, met with in the blood after death or some time after removal from the body, and exceptionally in the fresh blood. They were first detected in the bone-marrow.

Lymphatic Type.—Enlargement of lymphatic glands is the most conspicuous clinical feature. The leukocytes are usually less abundant than in the myeloid type. The lymphocytes predominate very greatly, but actual excess of large mononuclear forms and polymorphonuclear leukocytes is observed. Contrasted with myeloid leukemia the striking feature is the abundance of small cells—lymphocytes. The larger lymphoblasts are rarely conspicuous except perhaps in certain acute cases. Myelocytes occur in small numbers; exceptionally in consider-



Acute leukemia. (Drawing made under the direction of Dr. C. Y. White.)



Chronic lymphatic leukemia. (Drawing made under the direction of Dr. C. Y. White.)

able proportion. The number of red corpuscles is decreased and nucleated red cells may be present.

Acute Leukemia.—A separate description of acute leukemia is desirable, because in its clinical manifestations there are striking differences from those seen in chronic leukemia and because it is difficult to determine whether a given case is myeloid or lymphatic. In the rapid progress of the disease cells of great immaturity are cast into the circulation and opinions vary as to their nature. Some hold that these are lymphoblastic; others, that they are myeloblasts. Upon the whole, the latter view seems to be more tenable.

Acute leukemia seems, in some respects, a distinct type of the disease, and the symptoms are strongly suggestive of an infectious condition. The duration is usually from a few weeks to a few months after the first symptoms are noted. Gastro-intestinal lesions (ulcers in the mouth, stomach, and intestines) and hemorrhagic manifestations (purpura) are frequent. Moderate enlargement of the lymphatic tissues and infiltrations of the organs are discovered, and parenchymatous changes in the organs are constantly present.

The blood shows a varied picture. The total number of leukocytes may vary from a very moderate increase above the normal to several hundred thousands per cubic millimeter. Mononuclear elements are conspicuous, the predominating cell being one that resembles lymphocytes or lymphoblasts, and also the smaller myeloblasts. The nuclei are large, round, or horseshoe shaped, and stain faintly; the protoplasm forms a somewhat narrow rim around the nucleus. The polymorphonuclear cells and eosinophiles may be actually, but not relatively, increased in number; myelocytes are occasionally present. Considerable reduction in the number of red corpuscles is a usual feature of acute leukemia. Nucleated red corpuscles (especially normoblasts) are generally present.

HODGKIN'S DISEASE

This disease presents a certain superficial resemblance to leukemia in the enlargement of the lymphatic glands and sometimes of the spleen, and to a less extent in the histology of the lesions. As the differentiation has become more definite the old term *pseudoleukemia* has been generally abandoned.

Hodgkin's disease does not present an increase in the number of leukocytes in the blood, or, at most, a very moderate increase. There is a moderate but progressive anemia, with occasionally decided eosinophilia. In certain cases the polymorphonuclear elements are relatively excessive. The lymphatic glands enlarge more quickly than in leukemia, and the spleen and marrow are less frequently involved. (See Lymphatic Glands.)

Pseudoleukemia Infantum

Under this name von Jaksch described a form of leukocytosis, with enlargement of the spleen and liver, occurring in children. There is rapid

and excessive oligocythemia, and the leukocytosis is pronounced. Leucocytes of all types are present, and give to the blood a curiously variegated appearance. There is no striking difference, however, from the characters of the blood met with in other cases of leukocytosis in infancy. Rickets and congenital syphilis seem to be closely related to this form of disease.

The enlargement of the spleen and liver is not of the nature of that seen in leukemia, but is simply a chronic hyperplastic condition.

FOREIGN BODIES AND PARASITES

Foreign Bodies in Blood.—Various kinds of particles may gain access to the blood-current and may be carried to peripheral parts of the circulation. In anthracosis a lymphatic gland may attach itself and, after softening, rupture into a vein. The particles of carbon are thus distributed in the blood. Small portions of tumors, of the heart-valves, calcareous particles from atheromatous plates, and portions of thrombi are frequently transported by the blood. Charcot crystals are met with in leukemia, and pigment-matter, due to disintegration of the blood itself, is seen in malaria.

Parasites in the Blood.—Among the animal parasites are the malarial plasmodium, which occurs within the red corpuscles or free in the plasma; the *Schistosomum hæmatobium*, which occupies the portal vein; the embryos of the *Filaria bancrofti*, and the trypanosomes. (These are more fully described in the section on Parasites.) Portions of hydatid cysts or of cysticerci and trichinæ are occasionally conveyed in the circulation.

Vegetable Parasites.—Mould-fungi sometimes gain entrance into the circulation and lead to serious embolism, as does also the *Streptothrix actinomyces*. Of the pathogenic bacteria, the spirochete of relapsing fever and the bacillus of anthrax are most abundant in the blood. Other micro-organisms are more difficult of demonstration, though many kinds of micro-organisms have been demonstrated morphologically and in culture.

CHAPTER II

DISEASES OF THE LYMPHATIC TISSUES

THE SPLEEN

Anatomical Considerations.—The spleen is practically a complicated lymphatic gland with close relations to the circulation. It is enclosed in a fibrous capsule, from which trabeculæ enter into the substance of the organ and give off subdivisions that unite and form a framework, in the meshes of which lymphoid tissue is embedded. The splenic artery enters at the hilum and subdivides into numerous branches which traverse the trabeculæ. Side branches are given off from the trabecular arterioles; these penetrate the splenic pulp and are surrounded by denser aggregations of lymph-cells, which are visible to the naked eye as the Malpighian bodies. All of the terminal arteries discharge their blood directly into the spaces of the splenic pulp, from which it is re-collected into the veins. The spaces contain, in addition to lymphoid cells and red blood-corpuscles, larger cells, endothelial in type, often containing pigment granules or even blood-corpuscles.

The weight of the spleen in the adult varies from 140 to 200 gm.

The splenic function remains in doubt. It seems to have some connection with the process of manufacture of leukocytes, and is one of the sources of red blood-corpuscles in early life. It may also be the place of destruction of red corpuscles, and in cases of general hemolysis, or blood-destruction, the blood-pigment and fragmented corpuscles are especially arrested in this organ. It has something to do with the iron chemistry of the body. The muscular tissue of the capsule contracts and expands, assisting thus in the propulsion of blood and lymph.

Pathological Physiology.—The relations of diseases of the spleen to the general health are still obscure. It has been held by some pathologists that this organ plays an important part in the process of immunization or combating infectious diseases. The fact that bacteria and foreign bodies circulating in the blood are arrested to a large extent in the spleen warrants the suspicion that this organ is important in disposing of irritants, and thus preventing their gaining access to more vital parts. Experimenters, however, have found no uniform increase of susceptibility to micro-organismal inoculation on the part of splenectomized animals. For the present, therefore, we can only suspect that removal or disease of the spleen renders individuals more vulnerable to infections.

The effect of removal of the spleen in human beings is surprisingly slight. A certain amount of anemia and general deterioration of health follow the operation, but seem to be the result of the operation *per se*,

rather than of removal of the organ. Subsequently, complete health is regained. Some compensatory (?) enlargement of the lymphatic glands has been observed after splenectomy.

ABNORMAL DEVELOPMENT AND SITUATION

Complete absence of the spleen has sometimes been noted in children that lived for several years. More commonly slighter defects, such as unusual smallness or excessive lobulation, occur. Very often small accessory spleens, the size of a pea or a marble, are found, occurring chiefly in the abdominal cavity, but also found elsewhere.

Movable Spleen.—The organ may be quite movable, either as a congenital condition or as the result of enlargement and resulting traction upon its attachments. Downward displacement and movability are frequently found in cases of splanchnoptosis. Twisting of the pedicle of a movable spleen may lead to strangulation of the circulation and consequent necrosis.

CIRCULATORY DISTURBANCES

Anemia may occur in cases of general anemia resulting from hemorrhage or inanition. The spleen presents a contracted appearance, the capsule being wrinkled, and on section the substance is found to be lighter in color and the fibrous stroma is more prominent than normal.

Hyperemia may be active or passive. *Active hyperemia* is a physiologic condition during digestion, when the spleen increases somewhat in size. Intense congestion occurs in a number of diseases, but so commonly passes into inflammation that it will be described under that heading. *Passive congestion* is most marked in cases of cirrhosis of the liver, but also occurs in association with hyperemia of other organs as the result of cardiac failure, of emphysema, or of other diseases obstructing the larger venous channels. The spleen is greatly enlarged and of a dark-red color, and the capsule is often tensely distended; the Malpighian bodies are less distinct than normally. After long continuation of the process hyperplasia of the trabeculae and the fibrous stroma generally takes place. The spleen may be greatly enlarged and very dense at this stage. Subsequently contraction of the newly formed fibrous tissue may lead to atrophy of the proper splenic substance and increased induration of the organ (*cyanotic induration*). Considerable pigmentation is found in such cases from the destruction of the stagnated blood (see p. 448). H. A. Christian, in a study of the spleen in cases of chronic passive congestion and cirrhosis of the liver, found no change of any kind in the Malpighian bodies of the spleen. The pulp was relatively poor in cells and the blood sinuses generally dilated. There was also, as a rule, a definite layer of low cuboidal endothelial cells lining the sinuses. In a majority of the cases there was increase of the connective-tissue framework. In the 10 cases with no increase in connective tissue, the spleen felt almost equally firm, showing that

the firmness was due to vascular distention. The same factor probably enters into the production of firmness in all of the cases. Proliferation of the reticular tissue of the pulp with little or no change in the white fibrous and elastic tissue of the organ, constituted the main connective tissue change. An increase of connective tissue around the small splenic arteries and within the Malpighian bodies was sometimes seen.

Hemorrhages in the spleen may be the result of traumatism, when large hematmata may form, especially just beneath the capsule. Small areas of hemorrhage are not infrequent in intense infections with splenitis, but it is difficult to draw a line between hemorrhage and the overfilling of the spaces by congestion, since the blood under normal conditions enters directly into the splenic pulp.

Embolism of the splenic artery is very common in cases of endocarditis or thrombosis in the left heart or aorta. As the spleen contains abundant "terminal arteries," infarction is the common result. The area may remain light colored, constituting an anemic infarct; or it may become overfilled with blood, when hemorrhagic infarction results. In either case there is a wedge-shaped lesion, with the base toward the surface of the organ and the apex within, harder than the surrounding tissue and usually somewhat elevated. The swelling and elevation in the case of anemic infarction are partly due to a zone of hyperemia which usually surrounds it. Complete resolution may occur, but more commonly the area involved undergoes coagulation necrosis and softening, and as absorption takes place fibrous overgrowth gives rise to the formation of a scar. There may be numerous infarcts of small size or a single large one sometimes occupying as much as half of the organ. (Septic infarction and its results are discussed under Abscess of the Spleen.)

Thrombosis of the splenic vein may occur in association with thrombosis of the portal vein. It causes intense passive hyperemia of the spleen. Occasionally calcification of thrombi gives rise to the formation of *splenic stones*.

INFLAMMATION OF THE SPLEEN, OR SPLENITIS

Splenitis occurs in a variety of conditions, and may present itself in several forms, among which the acute enlargement of the spleen of infectious diseases and localized splenitis, or abscess of the spleen, are the principal.

Diffuse Splenitis.—The splenic enlargement of infection occurs particularly in typhoid fever, malaria, septicemia, typhus, and relapsing fevers; and less markedly in pneumonia, scarlet fever, small-pox, and influenza. In the earlier stage the spleen is simply congested and presents a dark-red color; is firm, and the capsule more or less distended. On section, the Malpighian bodies are usually obscured, and there may be visible areas of hemorrhagic extravasation. Microscopically at this stage the blood-vessels are all found overdistended, and the spaces within the splenic pulp are filled with red and white blood-corpuscles.

If the process has continued for some time, pigment masses and degenerated corpuscles are visible, but there are as yet no evidences of inflammatory hyperplasia of the splenic pulp or stroma.

As the process advances the spleen may become softer and may be quite diffuent. On section, the substance is now found to be lighter in color, the Malpighian bodies are distinct, and, particularly in violent septic cases, are decidedly prominent, presenting themselves as yellowish-gray punctæ, somewhat resembling miliary tubercles. The capsule of the organ may still be tensely distended, but in other cases is wrinkled, as if some shrinkage of the spleen had occurred in the change from the first stage of congestion to that of well-defined inflammation. Microscopically there is now apparent a great increase of the cells of the splenic pulp, particularly of those constituting the Malpighian bodies. That this increase is partly at least due to active proliferation is known from the abundance of mitoses. There is also hyperplasia of the stroma and trabeculæ, and of the endothelial cells of the spaces.

In still later stages signs of degeneration may become prominent. This is apparent in the increasing softening of the organ, while under the microscope there are found cellular degenerations leading to the formation of detritus, to fragmentation of the nuclei of the cells, and to pigmentation by disintegration of red blood-corpuscles.

Terminations.—Most frequently complete resolution occurs. Sometimes, however, persistence of the inflammation is noted; and, when repeated attacks of the infection occasion repeated attacks of splenitis, chronic inflammatory hyperplasia is the result. This is especially marked in the "ague-cake" spleen of malaria. Spontaneous rupture or rupture from slight trauma may result from the softened and distended condition of the organ. Finally, suppuration may ensue, either in the form of a diffuse softening and purulent infiltration of the entire organ, or in the form of a localized abscess beginning at the point of greatest involvement.

Circumscribed Splenitis, or Abscess of the Spleen.—This may be the termination of an acute diffuse splenitis, particularly in septicæmia and typhoid fever; or it may be caused by extension of diseases of neighboring structures, by septic embolism, or traumatic injuries. In the last case, the mechanical injury of the spleen merely furnishes suitable conditions for the action of bacteria conveyed to it through the circulation, or the spleen is actually penetrated and infected. Occasionally abscess may result from the perforation of gastric ulcers or from the extension of other inflammations in the vicinity. An important group of cases is that in which the abscesses are embolic and metastatic (Fig. 181). Such cases are met with in malignant endocarditis or thrombosis of the heart or aorta, and in cases of pyæmia following other infective conditions. The first effect of the embolism is a hemorrhagic or anemic infarction, but this soon undergoes suppurative softening, beginning at the apex of the infarct. Metastatic abscesses are most common near the surface of the organ and are usually multiple, though a single cavity occupying the greater part of the organ may occur.

Small collections may become absorbed or inspissated, leaving a necrotic or cheesy collection as a residue. Larger collections may be discharged by perforation into the stomach or intestines, or they may break into the peritoneal or pleural cavity, causing septic peritonitis or pleuritis.

Chronic Inflammation or Chronic Hyperplasia of the Spleen.

—Attention has already been called to the slow hyperplasia of the connective tissue and sometimes of the splenic pulp occurring in consequence of chronic passive congestion and of repeated attacks of acute splenitis. The spleen is large in size and firm. The capsule is often tensely distended and may be greatly thickened. The thickening is either diffuse or circumscribed, patches of almost cartilaginous hardness occurring in the latter case. Attachments by fibrous adhesions may fix the spleen to the diaphragm or the neighboring organs. On section the spleen is found dark in color from the presence of abundant pigment, and the excess of fibrous tissue may be visible to the naked eye. Microscopically, increased thickness of the fibrous trabeculæ, hyperplasia of the connective tissue about and within the follicles and that of the walls of the small blood-vessels, and pigmentation with altered blood-pigment are the conspicuous features.

A somewhat different form of chronic hyperplasia is dependent upon syphilis, especially upon the congenital form. In this the appearances are much the same as in the cases following splenitis or congestion, but, as a rule, the color is somewhat lighter from the fact that the process is a slowly hyperplastic one without acute inflammatory or congestive manifestations. Somewhat similar appearances result from rickets. The indurative processes in the spleen following cirrhosis of the liver may be due at times to thrombosis of the liver veins, but this does not always exist. It has been suggested that circulating toxins are responsible.

Splenic Anemia; Splenomegaly.—These terms have been used to describe a clinical condition distinguished by chronic enlargement of the spleen due mainly to fibrosis beginning in the follicles, gastro-intestinal disturbances, a tendency to hemorrhages from the stomach, and later by progressive weakness and ascites. Anemia of chlorotic type may occur, especially in the hemorrhagic cases, but is not essential, and the name "splenic anemia" is, therefore, ill chosen. The development of



Fig. 181.—Embolic abscess of the spleen (from a specimen in the Museum of the Philadelphia Hospital).

ascites is due to secondary cirrhosis of the liver. Cases presenting this association are designated *Banti's disease*.

The so-called *primary* or *idiopathic splenomegaly* of Gaucher is an enlargement of the spleen due to accumulations of endothelial cells without much cirrhotic change, associated with enlargement of the liver, anemia, and pigmentations of the skin, or hemorrhages. The liver and lymph-glands may show the endothelial changes as in the spleen.

The etiology and nature of these cases is probably varied. At autopsy some show merely chronic congestion of the spleen, others a more definite chronic hyperplasia, a few have been found to present a peculiar proliferation of the endothelium of the sinuses (see Tumors). Formerly splenic anemia was regarded as a splenic type of Hodgkin's disease. This view has been disproved by the absence of the usual histological features of the latter disease.

ATROPHY AND DEGENERATIONS

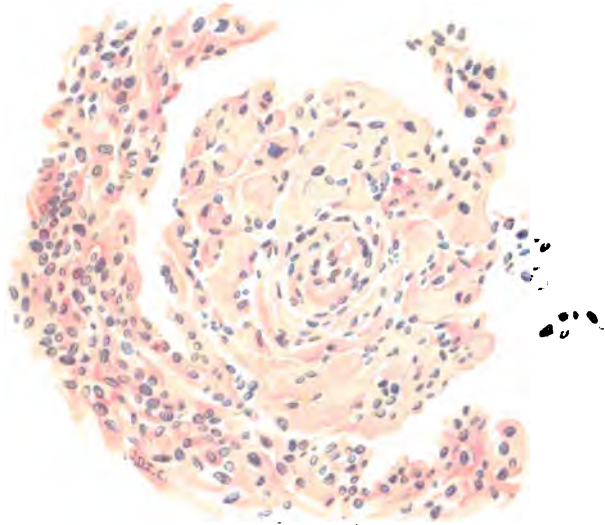
Atrophy of the spleen is very common in old age. The capsule is usually wrinkled and somewhat thickened, and on section the organ is more fibrous in appearance on account of atrophy of the splenic pulp and proliferation of the stroma. Thickening of the capsule sometimes appears in the form of white plates of cartilaginous hardness, which result from inflammatory overgrowth of the capsule (*perisplenitis cartilaginea*).

Amyloid infiltration occurs more frequently in the spleen than in any other organ. The causes are those which lead to amyloid disease elsewhere. In most cases the degeneration begins in the Malpighian bodies, affecting the walls of the blood-vessels (Plate 5) and the lymphoid elements. On section in such a case there are seen small round areas about the size of a currant-seed, of gelatinous, translucent appearance. These have been likened to grains of boiled sago, and the term *sago spleen* is not inappropriate. In other cases a more uniform involvement of the whole organ is noted, and the section presents the appearance of boiled ham or dried beef (*bacony spleen*). Considerable enlargement of the organ is noted in such instances, and the tissue is much harder than normal. Beginning amyloid degeneration may be difficult to determine microscopically, but is readily demonstrated by the microscopical staining reactions. (See Amyloid Degeneration.)

Hyaline degeneration has been observed in association with amyloid and independent of the latter. It affects the small blood-vessels and the reticulum more particularly.

Pigmentation is a very common result of chronic congestion as well as of repeated acute splenitis; the spleen in cases of cirrhosis of the liver and in chronic malaria is, therefore, habitually pigmented. The deposit occurs first in the walls of the blood-vessels and later throughout the splenic structure, either within the cells or lying free in the tissue. Occasionally pigment particles derived from the external world are deposited in the spleen. This is especially true of dust particles which

PLATE 5



Amyloid degeneration of the spleen, showing a degenerated Malpighian body; specimen stained with hematoxylin and eosin.

have reached the circulation from softened bronchial glands. In cases of diseases of other kinds leading to discharge of foreign bodies or tissue elements into the circulation, the arrest not rarely occurs in the spleen, and reactive congestion or inflammation with enlargement of the spleen may result (*spodogenous splenitis*). Pigmentation of the spleen is seen in progressive pernicious anemia and other conditions in which hemolysis occurs. The pigments resulting from the destruction of red corpuscles are deposited in the liver, spleen, and other organs. Biliary pigmentation of the spleen occurs in various forms of jaundice. Pigment is removed or at least ingested by endothelium, lying along trabeculae and sinuses. Hematoidin is found in infarcts.

Calcification occurs in the thickened capsule of chronic splenitis and in old infarcts, tuberculous or syphilitic areas, and occasionally in thrombi of the splenic vein. Parasitic cysts may be surrounded by calcification.

LEUKEMIA AND HODGKIN'S DISEASE

The spleen is usually involved in leukemia and occasionally in Hodgkin's disease. The former condition is primarily an affection of the bone-marrow (myeloid type) or of the lymphatic glands (lymphatic type). In either case, however, the spleen is usually involved. In the earlier stages the organ is enlarged and soft, and on section exhibits evidences of intense congestion. Later, the characteristic hyperplasia of myeloid or lymphatic elements causes a lighter color or areas of lighter color between the more congested portions. Infarctions, sometimes of considerable size, and hemorrhagic or anemic and necrotic, may add to the variegated appearance of the surface of section. Histologically in myeloid cases there are found areas of myelocytic or myeloblastic hyperplasia, sometimes with giant cells and erythroblasts, characteristic of myeloid structure. In lymphatic cases abundant lymphocytes replace the normal splenic tissue.

In Hodgkin's disease the characteristic histological features (see Lymphatic Glands) may be found in the enlarged spleen.

TUMORS AND PARASITES

Sarcoma and Carcinoma.—*Primary sarcoma* of the round-celled or fibrosarcomatous variety has been observed. *Secondary sarcoma*, particularly melanotic sarcoma, is more common than the primary growth, and *secondary carcinoma* occurs.

Endothelioma.—A few of the cases of the clinical syndrome called splenic anemia have presented a remarkable proliferation of the endothelium of the splenic sinuses, and authors have variously regarded the process as an endothelial hyperplasia or as endothelioma. In a case reported by Stengel the process strongly suggested a tumor.

Cysts are occasionally discovered. They are small and are probably due to dilatation of the lymphatic spaces, or to atrophy and cystic degeneration of the Malpighian follicles.

Others are said to be due to an intracapsular injury and hemorrhage, with absorption of the solid parts and subsequent encapsulation. Lamina of clot may be found on the walls. Some authors believe that cysts may be due to an invagination of peritoneum.

Fibroma, angioma, and lymphangioma are very rare.

Parasites.—*Linguatula rhinaria*, echinococcus cysts, and cysticerci have been observed.

INFECTIOUS DISEASES

Tuberculosis of the spleen may occur in the form of minute miliary tubercles, which have a grayish translucent appearance, and are usually present in large numbers, especially near the capsule. They may be distinguished from enlarged Malpighian bodies by their greater opacity and their grayish rather than yellowish color. Tuberculosis also occurs in the form of larger caseous nodules, especially in children (Fig. 182). In these cases there are seen nodular masses the size of a pea or cherry studding the surface and deeper structure of the spleen. This form is called *Affentuberculose* by the Germans, from the resemblance of the large nodules to tubercles met with in monkeys. Histological examination proves the nodules to be composed of aggregations of tubercles undergoing caseation. Primary tuberculosis of the spleen has never been observed.



Fig. 182.—Large caseous tubercles in the spleen of a child (Orth).

Syphilis may present itself in the form of syphilitic gummata, which are usually multiple and may be either small or large. They are distinguished by their central degeneration or by the fibrous tissue striations at the exterior.

Diffuse hyperplasia of the spleen is a frequent or almost constant lesion of congenital syphilis.

The spleen is the seat of secondary deposits in actinomycosis, glanders, and leprosy, the lesions following the type characteristic for these diseases.

Perisplenitis.—The capsule of the spleen may be inflamed as a part of acute splenitis or from a peritonitis. It is usually of a fibrinous character and may resolve or continue into a chronic stage, in which case it may have adhesions to adjacent organs or extension into the trabeculæ, or both. The capsule becomes gray and opaque.

THE LYMPHATIC GLANDS

Anatomical Considerations.—The lymphatic glands or nodes are accumulations of lymphadenoid tissue enclosed in a fibrous capsule,

into which a number of small afferent lymphatic vessels enter, and from which a somewhat smaller number of larger efferent lymphatic vessels emerge. The nodes are composed at the periphery of spherical lymphatic follicles made up of lymphadenoid tissue, and at the center of medullary cords of the same structure. Under the outer capsule and alongside of the fibrous trabeculae which dip down between the follicles and cords are spaces lined with endothelial cells, the lymph-sinuses. Through this system of channels the lymph conveyed by the afferent vessels filters to the hilum of the glands, where the efferent vessels take their origin. Histologically, the lymph-follicles present at their centers collections of somewhat large and pale-staining cells with numerous mitotic figures. These are the germ centers composed of *lymphoblasts*. Surrounding these are smaller and more deeply staining cells—lymphocytes.

Functions of the Lymphatic Glands.—Two important functions of the glands are recognized: a filtering action and blood-cell formation. The filtering action of the glands is readily explained by the anatomical features described, and is exhibited by the accumulation of bacteria or pigment in the lymphatic glands adjacent to an infective lesion or a source of pigmentary deposit. What part the regional lymphatic glands may play in the local inhibition of infective processes by destroying micro-organisms arrested by them is a matter of theory rather than present knowledge.

The blood-cell formation of the lymphatic glands is concerned with the production only of lymphocytes and the plasma-cells. Both of these cell forms are apparently derivatives remotely of the endothelium of the lymphatic vessels or sinuses, and more immediately of lymphoblasts. The lymphocytes are relatively small cells with deeply staining nuclei, a marked nuclear membrane, and a somewhat granular basophilic protoplasm. These are derived from *lymphoblastic cells* (such as are seen in the germ centers of the follicles)—larger cell forms with paler nucleus and protoplasm. From these forms under pathological conditions may be derived *plasma-cells*, which are mainly distinguished by the eccentric position of the nucleus and the deeply staining (basophilic) protoplasm. These cells are especially abundant in the round-cell infiltration of inflammation.

Hemolymph Glands.—Certain of the lymphatic glands of the retroperitoneal region differ from ordinary lymphatic glands in having blood-sinuses instead of lymph-sinuses. These have been termed "hemolymph glands." Such glands are less frequently found in other situations, such as in the mediastinum, thymus region, cervical region, etc. They are usually embedded in fat tissue, and, as a rule, are near the wall of some large vessel. The number and size of the blood-vessels connected with these glands are remarkable, showing the relation to the hemic circulation. Transitional conditions between the typical lymphatic gland and the hemolymph gland are met with. Some of the glands resemble splenic tissue, and others the marrow tissue. Warthin suggests the terms "splenolymph" and "marrow-lymph gland." Pathologically these glands have been found congested or showing evidences of increased pigment formation in various types of anemia. They appear to have an active hemogenic function in such conditions.

ATROPHY

This condition of the lymph-glands occurs in old age and in various marasmic conditions. The glands suffer considerable diminution in size, the cellular elements being particularly affected; they are, therefore, hard, dry, and often irregular in shape. Fatty infiltration may occur simultaneously with atrophy, the gland in such cases preserving its size and having a decidedly fatty appearance.

HYPERTROPHY

This is so closely allied to the conditions designated by the name of "lymphoma" that it is difficult to separate the cases which might be considered as strictly hypertrophy. In cases of experimental or surgical splenectomy, hypertrophy of the lymphatic glands has been observed. Chronic enlargement of the tonsils and generalized lymphatic enlargement in *status lymphaticus* may also be considered as forms of hypertrophy.

STATUS LYMPHATICUS

This condition is one in which there is a marked preservation after early infancy or childhood of the relative excess of lymphatic tissue that characterizes the earlier years of life. A pronounced feature of the anatomy of childhood is the richness in lymphatic tissue and the high percentage of lymphocytes in the blood. After the first few years, but especially after puberty, this excess of lymphadenoid structures disappears, but in certain individuals it persists. In such cases the term "status lymphaticus" is applied. Formerly this condition was regarded as closely identified with status thymicus, in which persistence of the thymus gland after the time of its normal atrophy is met with. Certain recent authors separate the two conditions, and certainly status lymphaticus is much more frequently unaccompanied by persistent thymus than accompanied by it.

Among the physical features of the lymphatic status are hypertrophies of the lymphadenoid tissues of the pharynx, the back of the tongue, the nasal passages, enlarged tonsils, cervical lymphatic glands, Peyer's patches, etc. The blood-vessels are usually hypoplastic and the heart may be in the same condition. Enlargement of the spleen and a persistent thymus may be found. The blood presents the infantile excess of mononuclear elements (mononucleosis), especially lymphocytes; in some cases the bone-marrow remains persistently infantile (red) in type. In recent years particular attention has been called to a lack in development of the chromaffin system. The adrenals are deficient and the other structures containing chromaffin elements are more or less defective. To this lack of chromaffin substance, and the consequent deficiency of its secretions (adrenalin, etc.), may be due the low tension of circulation, and perhaps sudden death, which sometimes occurs.

Certain writers describe as a separate form from the type above discussed, and which they regard as *primary status lymphaticus*, a *second-*

ary form which is developed in childhood or, later, in persons who had previously shown no abnormal structural conditions. Such secondary forms are said to occur as a result of rickets, syphilis, tuberculosis, and other infections, asthma and various diseases of the glands of internal secretion, such as Addison's disease, Graves' disease, myxedema, etc. The physical peculiarities are the same, but less pronounced than in the primary form. Rather too much weight seems to us to have been given to the blood condition (mononucleosis; lymphocytosis) in suggesting the existence of a status lymphaticus in some of these diseases.

DEGENERATIONS

Fatty infiltration is sometimes seen in cases of general obesity and also, as before mentioned, in atrophy of the glands.

Amyloid infiltration is met with in cases of general amyloid disease, and particularly in the cases in which the intestines are affected. The lymphatic glands may, however, be independently involved in cases of tuberculosis attended with suppuration. In such instances the adjacent lymphatic glands are most likely to suffer amyloid change. The morbid process rarely leads to marked alteration of the glands, but the amyloid material may be demonstrated by the staining reactions peculiar to it. The connective tissue of the trabeculæ and around the blood-vessels is first affected; later, the endothelial cells.

Hyaline degeneration has been observed. It affects the blood-vessels and connective tissue of the glands.

Calcification not infrequently forms the terminal condition in cases of necrosis or induration of the glands in consequence of tuberculous or simple inflammation.

There may be small calcareous granules scattered through the gland, or the entire gland may be infiltrated.

Necrosis may occur in consequence of tuberculous or syphilitic affections, or of simple inflammation. In the former cases, particularly in tuberculosis, the center of the gland or the entire gland becomes cheesy and soft, often liquefying and discharging the contents by rupture of the capsule. In consequence of simple inflammation, as in certain infectious fevers (typhoid, diphtheria, scarlet fever), a different form of necrosis is met with, areas of the gland becoming soft, pultaceous, and sometimes putrid. The gland may rupture, discharging its contents, or absorption of the liquid with inspissation and a pseudo-caseous form of degeneration may result. Finally, the degenerated area may become calcareous.



Fig. 183.—Anthracosis of a bronchial lymph-gland (Orth).

Pigmentation may follow acute inflammations or traumatism of the glands, the extravasations of blood occurring in such conditions leading to hematogenous pigmentation. The blood-pigment occurs in granular masses within the cells of the stroma or within the lymphatic cells themselves. Blood pigmentation may also occur in the glands adjacent to areas of hemorrhagic extravasation, the pigment in such cases reaching the glands through the lymphatic vessels and being deposited in the lymph-sinuses, or even in the follicles and cords. Analogous pigmentation from external sources may result from tattooing, and occurs regularly in the bronchial glands as the result of the inhalation of various dust-particles which penetrate the walls of the bronchioles and alveoli, and eventually find their way to the bronchial glands through the lymphatic stream (*anthracosis*) (Fig. 183). The glands may be completely black in such cases, and the lymphatic circulation through them may be obliterated. Secondary inflammatory changes result in most cases (see p. 455).

INFLAMMATION; LYMPHADENITIS

Acute lymphadenitis is commonly secondary to inflammations in the neighborhood, the irritants being carried by the afferent lymphatics. Sometimes direct extension of inflammation by contiguity of structure may lead to involvement of the lymphatic glands. Occasionally lymphadenitis is seemingly primary in cases in which the infective irritants have caused no lesion at the portal entrance to the body.

Pathological Anatomy.—The glands become enlarged, hyperemic, and considerably infiltrated with liquid. When the inflammation is intense there may be minute hemorrhages. Microscopically, the lymph-sinuses are found distended with cells—leukocytes, red blood-cells, and proliferated and desquamated endothelial cells from the lining membrane of the sinuses. The follicles and cords are increased in size from infiltration and probably also from proliferation of the lymphoid cells. The process may become arrested and resolution to the normal condition may ensue. If mild inflammation of this character has continued for a great length of time, or if the condition is repeated, hyperplasia of the trabecular connective tissue, of the blood-vessels, and of the capsule of the gland may lead to a termination in chronic enlargement and induration of the glands. The changes in the sinuses are spoken of as “sinus catarrh.” The proliferated lining endothelial cells in some places dominate the field. They may have more than one nucleus; they are actively phagocytic.

In cases of greater intensity of the infective cause, necrotic or suppurative changes may occur. In the cases of necrosis such as occur in typhoid fever and in diphtheria there may be noted small spots of yellowish-white color in the hyperemic glands, and subsequently these undergo well-marked necrosis. Complete necrotic softening and even rupture of the gland may ensue, or, if the necrosis remains limited in

extent, inspissation and sometimes calcification may terminate the process.

Suppurative lymphadenitis is not uncommon. It is seen in the glands below Poupart's ligament in cases of infective wounds of the leg; in the inguinal glands as a result of chancroid or gonorrheal urethritis; in the glands of the neck in association with diphtheritic, scarlatinal, or other inflammations of the throat, or following erysipelas; in the axillary glands as a result of wounds of the arm; and in the internal lymphatics in various infective diseases. The term *bubo* is applied to suppurative lymphadenitis of superficial glands. Of particular interest is the tendency to this condition in the plague of the East, or the bubonic plague (*q. v.*).

Pathological Anatomy.—The changes noted in the gland at the outset are similar to those in the simple inflammations, but under the microscope a greater accumulation of leukocytes is apparent, and the gland tends to soften, with the formation of more or less creamy pus. The capsule may prove resistant for a time, and reactive inflammation around it may establish an additional wall. A single gland of a group may be affected, but more commonly the several glands are together involved. Eventually rupture may take place, but in instances in which the process has been circumscribed, inspissation of the pus and, finally, calcification may occur.

In the most intense forms of lymphadenitis hemorrhagic or gangrenous conditions are developed. These acute inflammations usually have associated with them an infiltration and edema in the surrounding tissues (perilymphadenitis).

Chronic lymphadenitis leads to induration with enlargement. It occurs as the result of repeated acute attacks or in consequence of long-continued irritation by particles carried to the lymphatic glands from some focus of disease.

Pathological Anatomy.—As a rule, the process affects the connective-tissue elements of the gland in particular, and there results a considerable amount of induration, sometimes associated with atrophy or necrosis of the proper lymphoid structure. Occasionally, however, the lymphoid elements themselves are hyperplastic, and the normal relation of fibrous tissue, follicles, and medullary cords is preserved.

Microscopically, the overgrowth of the connective tissue springing from the trabeculæ, around the blood-vessels, and of the reticulum of the pulp is apparent. This may consist of round cells and fibrous connective tissue, or there may be a tendency to the formation of epithelioid cells and even giant cells.

Pathological Physiology.—Inflammations of the lymphatic glands are the result of the arrest of irritants of various sorts carried to the glands in the lymphatic channels. This arrest not unlikely serves the purpose of a protection against general dissemination of irritants, and may be of great importance in this way. Complete occlusion of the lymph-sinuses by deposition of solid particles (as coal-dust) or by disease of the glands may obstruct the lymphatic flow entirely, and a

retrograde inflammatory process may result from the damming back of infected lymph or from extension of disease along the lymphatic channels.

INFECTIOUS DISEASES

Tuberculosis of the lymphatic glands is due in nearly all cases to infection by bacilli reaching the gland through the afferent lymphatics, though occasionally hematogenous infection occurs. Under the heading "tuberculosis" we must include what the older writers designated as scrofulous glands, for in the majority of such cases, if not in all, the disease is essentially tuberculosis, though the mode of infection is not always apparent.

Pathological Anatomy.—The first visible change is the formation of small grayish nodules in the gland, and sometimes the eruption of these

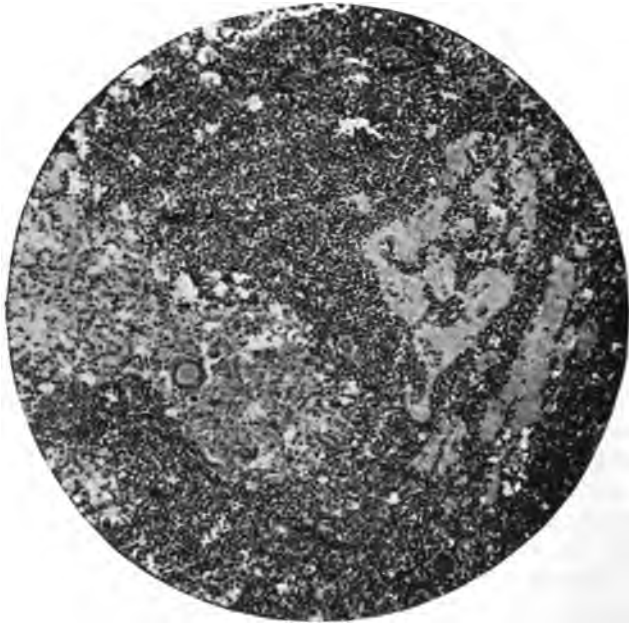


Fig. 184.—Tuberculosis of lymph-gland, showing early miliary tubercle and hyaline connective tissue.

is attended with hyperemia and inflammation. Later, these tubercles increase in size and undergo caseous changes (Fig. 185) as elsewhere, and eventually the entire gland may be converted into a cheesy mass, which may liquefy and not rarely discharges through the ruptured capsule. Microscopically, the first appearance is that of gray tubercles containing giant cells and epithelioid cells, surrounded by a zone of round cells (Fig. 184). Later, the characteristic appearances of hyaline transformation and of caseation are observed. Sometimes the glands in tuberculosis become enlarged and harder than normal, and present

areas of grayish color, but do not tend so markedly to undergo necrosis. In these instances the microscopical examination presents foci composed for the most part of epithelioid cells, and much less abundant in

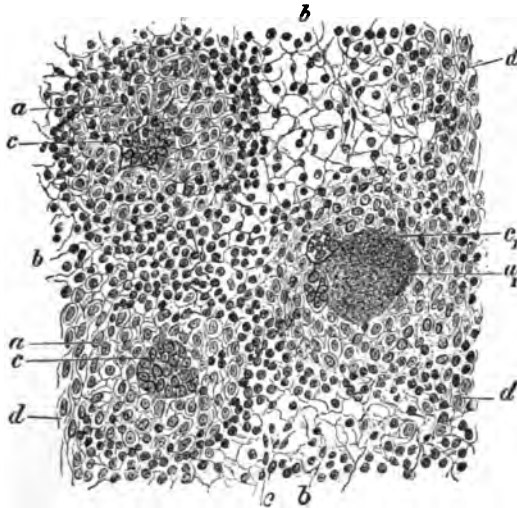


Fig. 185.—Tuberculous lymphatic gland: *a, a*, Recent tubercle with giant cell (*c, c*); *a₁*, caseous tubercle with giant cell (*c₁*); *b, b, b*, lymphadenoid tissue; *d, d, d*, epithelioid cells (Ziegler).

round cells than are tuberculous tissues as a rule (Fig. 186). Giant cells may be wanting, or a few may be found on prolonged search. The histological picture in these cases somewhat suggests sarcoma, and

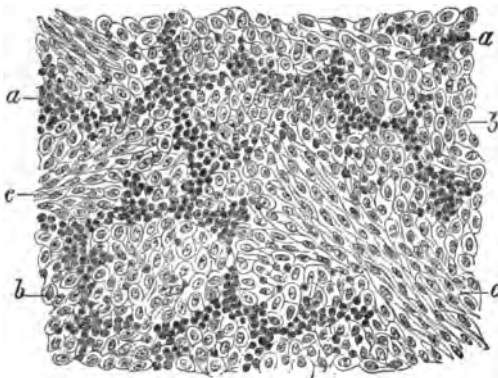


Fig. 186.—Tuberculous lymphatic gland: *a, a*, Lymphadenoid tissue; *b, b*, large round cells (epithelioid); *c, c*, large spindle cells (Ziegler).

the clinical as well as pathological findings have led some to regard cases of this type as Hodgkin's disease, and erroneously to conclude that Hodgkin's disease is really a form of tuberculosis of the lymphatic glands.

Scrofula.—The tuberculous nature of scrofulous lymphadenitis was first shown by demonstrations of the infectiousness of the softened glandular material when injected into animals. The micro-organisms themselves may be demonstrable in the earlier stages in the epithelioid or giant cells, or lying between these; but when the process is at all advanced it is extremely difficult or impossible to demonstrate bacilli.

Individual Groups of Glands.—Among the more commonly affected groups of glands are the cervical (Fig. 187), the bronchial, and the mesenteric. Tuberculous cervical glands occasion considerable tumors



Fig. 187.—Tuberculous lymphadenitis of the cervical glands (from a case in the Children's Hospital).

in the neck, and it is these in particular that have been classified as scrofulous. Not rarely they advance to complete softening and rupture on the surface. Sometimes, however, they penetrate deeply, and may rupture into the trachea or esophagus, or into the pleural cavity. The mode of infection is rarely apparent, but in many cases no doubt the micro-organisms enter through the mucosa of the mouth or pharynx, or the tonsils, where they may or may not first occasion specific lesions.

The bronchial glands are affected very frequently in cases in which the bacilli, entering through the lungs, have left no trace of tuberculous disease at the portal of entrance; while in cases of actual tubercu-

losis of the lungs the bronchial glands are quite constantly involved (Fig. 188). The glands are usually cheesy and may become calcareous, but softening not rarely occurs. Perforation of one of the bronchi may lead to acute bronchogenetic tuberculosis of the lungs; or the softened gland may discharge into a large vein and thus occasion disseminated miliary tuberculosis.

The mesenteric glands are especially involved in children, this condition being known as *tuberculosis mesenterica*. The infection occurs through the intestinal tract, and has sometimes been shown to be due to the ingestion of infected milk or meat. The intestines may first suffer, or the bacilli may penetrate the intestinal mucosa without causing local lesions.

Syphilis.—Enlargement of the lymphatic glands may occur in the vicinity of the initial lesion during the primary period; and is habitually present in all parts of the body during the secondary period, the post-cervical, axillary, inguinal, and epitrochlear groups being most characteristically involved. The glands are hard, and do not tend to soften or suppurate. Microscopically, there is found proliferation of the connective-tissue elements throughout the gland, with some endothelial hyperplasia, giving pictures very suggestive of tubercles minus giant cells.

In the tertiary period *gummata* (*bubo tertiaris*) may be observed, especially in the lymphatic glands adjacent to the diseased viscera.

Leprosy and actinomycosis occasionally involve the lymphatic glands. (See General Pathology.)



Fig. 188.—Tuberculous lymphatic glands at the bifurcation of the trachea (from a specimen in the Museum of the Philadelphia Hospital).

LEUKEMIA AND HODGKIN'S DISEASE

It is difficult to classify these diseases, which in some respects appear to be related to pure *hypertrophies*, while in other features (mainly clinical) they suggest infections. Finally, there are certain facts which indicate a close kinship with tumors, as, for example, the similarity in histological features, the malignant nature of the diseases, the widespread lesions (metastasis?), and the fact that certain accepted tumors (chloromata) are accompanied by a leukemic character of the blood. For all of these reasons leukemia and Hodgkin's disease are here considered between *hypertrophy* and *infections* on the one hand, and *tumors* on the other.

Leukemia.—The lymphatic glands are especially involved in the type of leukemia designated lymphatic, which usually, if not always, originates in the lymphatic glands. The view formerly held by many that all forms of leukemia originate in the bone-marrow was based upon an erroneous interpretation of the derivation of the cells in the blood and bone-marrow in certain cases. These cells, instead of being lymphocytic, were myelocytic in nature, and the supposed lymphocytic process is now recognized as myelocytic or myeloblastic.

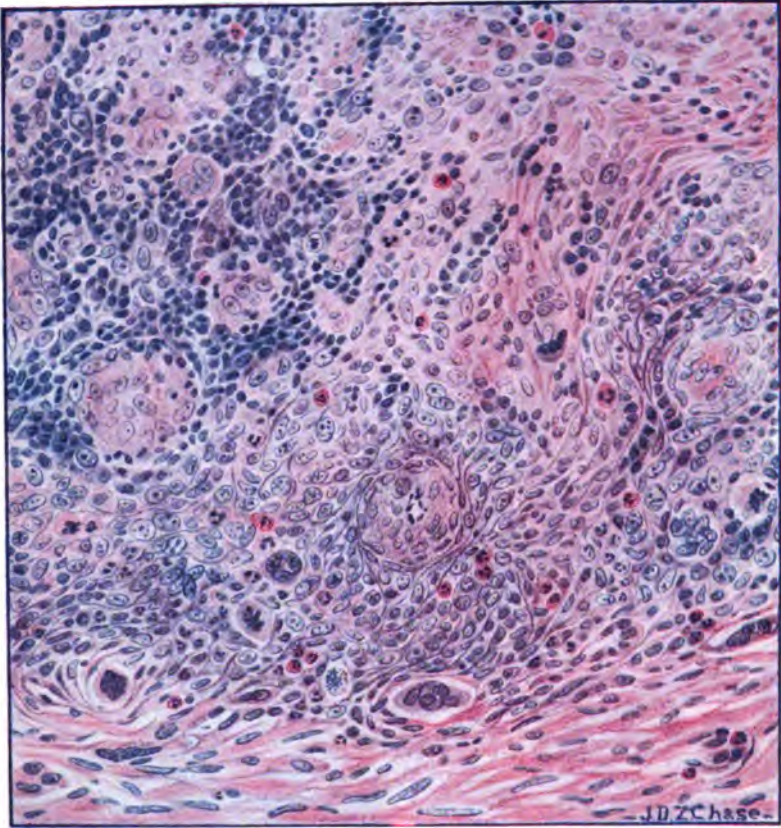


Fig. 189.—Hodgkin's disease, showing marked enlargement of the glands of the right axilla, with consequent dropsy of the arm; less marked involvement of the submaxillary, cervical, and inguinal lymph-glands.

The glands in lymphatic leukemia may be uniformly large in all parts of the body, or those of certain groups, such as the cervical, axillary, mediastinal, or inguinal, may be specially involved. Macroscopically, the glands are usually fairly firm, sometimes quite hard, or in other cases soft; are not greatly fused together when a whole group is affected; and on section the substance presents a grayish, pinkish to yellowish color. Areas of softening or hemorrhage may occur in exceptional cases.

Histologically, the whole gland is uniformly infiltrated with lymphocytic and lymphoblastic cells closely packed together and eradicating

PLATE 6



Hodgkin's disease of the Reed type. The illustration shows various stages of the disease process. In the upper left corner there is hyperplasia of large epithelioid cells among the small lymph-cells. To the right of this, in what is probably a sinus, there is hyperplasia of the large mononuclears, an excess of eosinophiles, fibroblasts, and fibers. Below these two sections of the picture are found masses of large mononuclears, separated by a connective-tissue framework, in which are also polymorphonuclears, eosinophiles, and polynuclear cells. At the bottom there is great increase of the fibrous tissue surrounding and distorting the cells.



all signs of the normal structure of the gland (follicles, medullary cords and sinuses). Sometimes the gland may be only partially involved, and the unaffected portion may then exhibit more or less normal histological features. The walls of small blood-vessels are frequently penetrated by the lymphocytic proliferations, which perhaps accounts for the entrance of the cells into the circulating blood. Similar histological features are found in the spleen and bone-marrow, and to a less extent in the liver and various other organs.

Certain investigators have described cases with precisely the same histological features, but without the leukemic blood-picture, and have proposed names such as *aleukemic lymphadenia* or *lymphadenosis*. That such cases may occur is easily understood when it is recalled that the blood-picture may become practically normal, either spontaneously or under treatment, without any notable change in the size of the glands or spleen.

Hodgkin's Disease.—It is difficult to define this affection accurately, either clinically or pathologically, though a certain histological picture seems to be fairly distinctive (Plate 6).

Macroscopically, Hodgkin's disease presents considerable enlargements of certain groups of lymphatic glands, notably the cervical, axillary, and inguinal. Other groups may, however, be similarly involved. The glands are more or less fused together, though rarely to a single uniform mass. Exceptionally, the glands may be quite separate from one another. On section, the substance is more or less firm, of yellowish or grayish color, and not infrequently exhibits areas of necrosis. Histologically, there are found numerous elongated (fibroblastic?) cells, often arranged in a somewhat trabecular manner, between which lymphocytic elements are found in variable abundance. In some cases the most striking feature of the histological picture is the large number of eosinophile cells seen in the section. Giant cells are sometimes fairly numerous. There is a fine fibrosis between the cells. Here and there will be found a large palely staining cell like a large endothelial cell, sometimes with more than one nucleus or occasionally a ring of nuclei, suggesting an origin from the compression of a lymph-channel.

Similar histological features are observed in the lesions of the spleen and liver met with in Hodgkin's disease.

TUMORS

LYMPHOMA, LYMPHADENOMA; LYMPHOSARCOMA

Lymphoma or **lymphadenoma** is a benign tumor affecting the lymphatic glands of a single group, or occurring in a more generalized form. Masses, sometimes of considerable size and of variable consistency (*hard* and *soft lymphoma*), are formed, but the process does not extend to surrounding tissues nor by metastasis to distant parts. Histologically, the growth presents the usual features of lymphadenoid tissue with more or less conspicuous hyperplasia of the reticular cells and endothelia in some cases (*hard lymphoma*).

It is extremely difficult to differentiate these growths from chronic lymphadenitis or lymphatic hypertrophy. The basis on which the distinction is made is rather the absence of adequate cause and the excessive growth of the glandular enlargements than any histological features. It must be recalled that very marked enlargements of lymphatic glands may be found in the neck or elsewhere in association with long-continued irritations, such as bad dentition or oral infections. In these cases it is difficult to determine whether the glandular process is inflammatory, infectious, or neoplastic.

Lymphosarcoma differs from lymphoma mainly in its manifest tendency to extend beyond the limits of the affected gland or group of glands to surrounding structures, and by metastasis to various parts of the body. The histological structure differs from that of lymphoma only in the less typical features of lymph-gland architecture. There is less differentiation of follicles, sinuses, and a more uniform undifferentiated lymphadenoid structure. Lymphosarcomata are especially common in early life, and occur in the cervical glands, tonsils, and mesenteric glands. Chloroma (see pp. 188 and 466) is a closely allied form of growth characterized by its greenish color.

Endothelioma of the lymph-glands may occur, according to Ewing, but it is difficult to determine in any given case whether it be truly neoplastic or secondary to a granulomatous disease of the nodes. A long-continued inflammation of the gland may occasion a neoplastic growth of the endothelium and overshadowing or obliteration of the lymphadenoid tissue.

Sarcoma.—Other forms of sarcoma are sometimes met with as primary localized new growths of the lymphatic glands. Such are not rarely seen in the mediastinum. In these instances the capsule of the gland is penetrated and local extension to neighboring glands and other surrounding structures is commonly observed, but the entire group of glands is not, as a rule, affected. General metastasis may occur, but affects the larger organs rather than the lymphoid tissues. Round-cell, spindle-cell, alveolar sarcoma, and endothelioma are the forms described. Secondary sarcoma occasionally involves the lymphatic glands.

Carcinoma is always secondary, the regional lymphatic glands being the most frequent seat of secondary cancer. The metastatic deposits are first seen in the peripheral lymph-sinuses of the gland, but later enlarge and may invade the whole gland or spread beyond the capsule.

BONE-MARROW

Anatomical Considerations.—The marrow of the bones is a tissue composed of a reticulum of connective-tissue cells, supporting a rich network of capillaries and venules of unusual width. The cells proper of the marrow are rounded and vary greatly in size. They contain a clear nucleus, a slightly acidophilic protoplasm, and many of them neutrophilic granules. In addition to these *myelocytes* there are occa-

sional giant cells (*megakaryocytes* or *myeloplaxes*) lying near the bony trabeculae; also nucleated red corpuscles, non-nucleated red corpuscles, and large cells enclosing corpuscles. After the first few years of life the marrow of the long bones loses its reddish color and becomes more or less yellow, and there is then found, microscopically, a great preponderance of fat-cells. The marrow of the vertebrae, sternum, ribs, and other flat bones remains more or less red throughout life, and islands of red marrow tissue may also be found in the marrow of the long bones in later years.

The marrow cells are descendants of the endothelial cells of blood-vessel walls. From these are derived somewhat large rounded cells containing a relatively large nucleus and having a basic non-granular protoplasm. These cells, termed *myeloblasts*, are the mother-cells from which the *myelocytes* (neutrophilic, eosinophilic, and basophilic) take their origin. This stage of the process of marrow-cell and blood formation is seen only in the latter months of fetal life and for a short time after birth; and pathologically in certain diseases affecting the blood. Soon after birth the myeloblasts are no longer found, and the myelocytes then represent the earliest phase in the process of leukocyte formation.

The red blood-corpuscles of the blood (erythrocytes) also trace their origin from the endothelial cells of blood-vessels. In the fetal marrow and under certain pathological conditions in later life may be found certain large hemoglobin-containing cells with a large pale nucleus (*primary erythroblast* or *megaloblast*) which are probably direct derivatives of the endothelial cells. In later periods of life a rounded, basophilic cell, containing a rather small and dark-staining nucleus, is the intermediary stage between the endothelial cell and the hemoglobin-containing erythroblasts. The latter also contain a darker and smaller nucleus than that of the "primary erythroblast." In the ultimate formation of non-nucleated red cells the nuclei of the erythroblasts undergo a process of pyknosis and karyorrhexis. The older idea of nuclear extrusion is probably incorrect.

In addition to the important rôle of blood formation the bone-marrow doubtless also plays some part in the defensive processes against foreign invaders. The large giant cells are occasionally greatly increased in size and number and exhibit active phagocytic properties in conditions attended with marked leukocytosis; myelocytes are greatly increased in number in certain infections, and sometimes myeloblasts become conspicuous. Finally, a more or less mechanical rôle may be indicated by the lodgment of large numbers of malarial plasmodia or other microorganisms in the marrow.

DEGENERATIONS

Fatty Infiltration.—The fat which occurs normally in the marrow may be excessively developed in conditions of general obesity, but also at times in marantic individuals, or as a result of atrophy of the bony tissues.

Mucoid degeneration is occasionally seen, and **necrosis** may form a part of the processes of inflammation.

Pigmentation occurs in the bone-marrow in cases of destruction of blood, as in malaria or various hemolytic toxemias.

ATROPHY

Atrophy of the bone-marrow is not infrequent in old age or in marasmic conditions. With this atrophy there may occur a gelatinous or mucoid transformation.

HYPERTROPHY

Hypertrophy of the bone-marrow occurs in various conditions in which an increased functional activity is required (1) to replace the cellular elements of the blood in case of hemorrhage or blood destruction, or (2) to provide greater numbers of certain cells in cases of infection. The gross appearance of the bone-marrow and its histological features differ considerably in different cases.

In anemic conditions resulting from repeated losses of blood or from hemolytic agencies the bone-marrow frequently exhibits a change from the adult (yellow or fatty) to the fetal or infantile type. In extreme cases the marrow of the long bones may be uniformly altered and sometimes is quite dark red in color; in less pronounced cases islands of pink or reddish color are scattered through the unaltered fatty marrow. The highest grade of transformation is seen in typical instances of pernicious anemia. Histologically, the marrow in the affected areas contains numerous nucleated red cells, many with mitotic nuclei, and also many myelocytes of different types and sometimes the primary myeloblasts. In pernicious anemia, in addition to these elements, there are found the primary erythroblasts or megaloblasts, and the spleen, liver, and lymphatic glands may contain areas of myeloid (myelocytic) tissue. The sharp distinction between various milder anemias and pernicious anemia here suggested is difficult to establish in many cases, and all investigators are not in agreement that there is a fundamental distinction, some holding that the marrow changes differ only in degree.

In infectious conditions, such as typhoid fever, pneumonia, streptococcus and staphylococcus infections, the marrow is the seat of marked changes. Areas of necrosis, degenerative changes in the blood-forming cells, and edema indicate the destructive effects of the infection, while hyperplastic processes are evidenced by large numbers of myelocytes, sometimes (especially in typhoid fever) myeloblasts and large numbers of phagocytic cells (megakaryocytes). Similar combinations of necrotic or degenerative processes and compensatory hyperplasia are found adjacent to metastatic tumors invading the bone-marrow.

The Bone-marrow in Leukemia.—The pathological changes in the bone-marrow as well as in other situations (liver, spleen, lymphatic

PLATE 7



Fig. 1.—Bone-marrow in pernicious anemia. Fig. 2.—Bone-marrow in leukemia.
(Kast and Rumpel.)

glands) are difficult to classify, but are included under the heading hypertrophy because the conspicuous feature in the histological changes is the hyperplasia of the blood-forming cells. It is difficult, however, to distinguish the lesions of the marrow from those in certain conditions quite generally recognized as tumors (myeloma, chloroma), and even the composition of the circulating blood may be quite the same in some of these cases (chloroma) as in typical instances of leukemia.

The bone-marrow in *myelogenous leukemia* presents a variegated appearance. Sometimes it is reddish, more often grayish or mottled, and occasionally quite yellowish (pyoid). Histologically, the conspicuous feature is the abundant hyperplasia of myelocytic cells. These, like the myelocytes in the circulating blood, may vary considerably in their size and staining reactions. The typical neutrophilic myelocytes are most abundant, but eosinophilic and basophilic forms, as well as non-granular cells and occasionally forms containing two different sorts of granules, may be observed. The red-corpuscle-forming elements are rather inconspicuous even in comparison with normal bone-marrow. In myeloblastic leukemia (formerly designated *acute lymphatic leukemia*) the basophilic myeloblasts form the predominating histological element.

The secondary foci of leukemic change (seen in the spleen, liver, lymphatic glands, and in various other organs) have a similar structure and represent local hyperplasia of marrow cells—either metastatic or originating locally from reversion of endothelial cells of the blood-vessels to their embryonal condition and potency.

In *lymphatic leukemia* the bone-marrow may present a quite similar macroscopical appearance, but histologically the myeloid elements are inconspicuous, while lymphoid cells constitute the bulk of the pathological areas. (See further under Lymphatic Glands.)

INFLAMMATION

Osteomyelitis, or inflammation of the marrow, is infectious in nature, and may occur in the course of various diseases, such as typhoid fever, relapsing fever, small-pox, septicemia, and the like; or as a result of traumatism and direct infection. Staphylococci and the typhoid bacillus (in typhoid cases) are the most frequent organisms encountered. The marrow disease may be the only expression of an infection which has arisen in an obscure manner (*cryptogenetic osteomyelitis*). In the cases occurring in the course of infectious diseases the changes are comparable to those which occur in the spleen under the same circumstances. The marrow assumes a redder color than normal, and it may be studded with punctate hemorrhages. In other cases areas of necrosis and granular degeneration of the cells may be present, and increased numbers of white blood-corpuscles may be discovered. Large phagocytic cells may be conspicuous. Sometimes the marrow is quite purulent. (See Diseases of Bone.)

TUMORS

The bone-marrow may be invaded by extension of tumors involving the bone, or may be the seat of metastatic growths, especially carcinoma. Greater interest, however, attaches to the primary tumors of the bone-marrow, which may be included under the general terms "myeloma" and "chloroma."

Myeloma.—This occurs in the form of multiple primary growths involving the vertebræ, ribs, and, somewhat less frequently, the long and flat bones. The growths are grayish, yellow, and sometimes pink or quite deep red in color; sometimes by confluence a uniform growth occupies the whole marrow cavity. The surrounding bone sometimes becomes eroded and spontaneous fractures may occur. Metastasis does not occur. Histologically, myelomata are usually composed of myelocytes (granular or non-granular), but in some cases have been made up entirely of plasma-cells (plasmocytoma). In rare instances erythroblasts may be conspicuous. Sometimes the tumor is greenish (myelocytic chloroma). The blood in myeloma rarely if ever presents leukemic features, but a striking clinical feature is the presence of Bence-Jones' albumin in the urine.

Chloroma.—This term is applied to tumors presenting a greenish appearance on section, and involving the bone-marrow as well as the lymphatic glands, thymus, and the lymphatic tissues along the gastrointestinal tract. The periosteum of the bones of the head and face is an especially common seat. Histologically, two forms may be distinguished: a *lymphoidal*, in which large lymphocytic cells make up the substance of the growth, and a rarer form, the *myelocytic*, in which the cells are of the bone-marrow type. The cause of the green color is unknown. Sometimes parts of the growths or certain of the metastases fail to present the green color seen elsewhere. An interesting feature is the leukemic character of the blood, which suggests the close relationship of leukemia to processes manifestly neoplastic.

CHAPTER III

DISEASES OF THE CIRCULATORY SYSTEM

THE HEART

Development of the Heart.—At the earliest period of fetal life the heart is represented by a hollow tube, lying toward the ventral aspect of the neck. Later this assumes an S shape, and still later a transverse constriction marks the position which the auriculoventricular grooves subsequently occupy. Finally, vertical grooves divide the lateral halves into the respective auricles and ventricles; and the *truncus arteriosus*, which is at one of the ends of the primitive tube, becomes divided into two parts, forming the pulmonary artery and aorta. The separation of the cavities within is accomplished by the outgrowth of septa springing from the walls of the primary cavities. The septum dividing the ventricles is the first to appear, and springs forward from the posterior wall. Next a budding is seen in the position which is later occupied by the tissue between the auriculoventricular orifices of the two sides; still later the auricular cavity is divided into two parts by a process beginning at the lower and posterior part. The septum which divides the *truncus arteriosus* is essentially connected with or is a part of the septum which separates the ventricles. All of these changes begin from the seventh to the ninth or tenth week of fetal life.

Anatomical Considerations.—The heart consists of three layers—the endocardium, muscular layer, and pericardium. The endocardium is the inner lining of the organ, and is composed of a layer of endothelial cells resting upon a stratum of connective tissue. It is continuous with the lining membrane of the arteries, and by duplications forms the valves. The muscle of the heart is arranged in layers which run in different directions—circular, longitudinal, and obliquely. There is no continuity of the musculature of the auricles with that of the ventricles, except in the case of the special muscle cells, which will be mentioned presently. The muscle of the two sides of the heart is in part continuous. Thus both auricles and both ventricles have certain muscle layers in common, but in part, especially in the ventricles, the musculature is wholly independent.

In recent years much attention has been given to a separate system of muscle cells or fibers (the Purkinje cells) which are found just beneath the endocardium in the auricles and ventricles. They are now known to make up a well-ordered system which begins with the sub-endocardial fibers in the right auricle where it is spread out widely. At the auriculoventricular junction it becomes contracted to a narrow band or cord (the bundle of His) which passes downward into the interven-

tricular septum, in the upper part of which it divides into a right and left branch. These branches run to the respective ventricles and their fibers spread out under the endothelium, and eventually extend to all parts of the musculature. This system, composed of somewhat less completely differentiated muscle cells than those of the body of the heart, is concerned with the conduction of impulses to contraction from the auricle to the ventricle. At two positions there are found nodes or massed cells of this tissue—one in the wall of the right auricle adjacent to the mouth of the superior cava, the other at the auriculoventricular junction. The former is now recognized to be the site where the rhythmic impulses that occasion the cardiac contractions originate.

The fibers of the heart muscle are peculiar in being branched and in being devoid of a sarcolemma. The pericardium resembles the endocardium in structure.

The blood-vessels supplying the heart muscle are branches of the coronary arteries. They divide and subdivide, and afford abundance of blood proportionate to the needs of so active an organ. Anastomosis between the ends of the myocardial vessels is by no means perfect, so that infarcts occur the more easily. The lymphatic system is equally developed. The nervous system includes numerous ganglionic centers in the furrows between the ventricles and between the auricles and ventricles. Other ganglion-cells are found within the muscle itself.

Details regarding the gross structure of the organ need not be mentioned here. The weight of the heart in the adult male is about 300 gm., in the adult female about 250 gm. The volume of the entire organ in the adult male is about 290 to 310 c.c., in the adult female about 260 to 280 c.c.

CONGENITAL DISEASES AND DEFORMITIES

Abnormalities of the heart may be discovered in the newborn and are the result of developmental defects or, less commonly, of fetal endocarditis and myocarditis. The older pathologists attributed to inflammatory changes many of the conditions which more accurate knowledge of the development of the heart clearly indicates are the result of defects in development.

Abnormality of Position.—The heart may retain its position high up toward the cervical region, and may even be entirely in the neck. Occasionally it is completely exposed or, merely covered with pericardium, lies immediately beneath the skin, the sternum in such cases being divided in the middle line. Sometimes it lies beneath the skin of the abdomen.

Abnormality in Size.—Congenital smallness, or *hypoplasia*, of the heart and aorta is occasionally observed. Particular attention has been called to this condition in cases of chlorosis (see p. 434).

Defective Development.—There may be complete absence of the heart in acardiac monsters. Sometimes the septa dividing the auricles and ventricles are wholly wanting and a *bilocular heart* results; or the auricular septum alone is absent, when the organ is *trilocular*. More

commonly than these conditions, the organ is completely reversed, lying on the right side of the body and having the blood-vessels entering it and leaving it reversed, so that the general venous blood enters the left auricle, the pulmonary blood the right auricle, while the aorta springs from the right ventricle and the pulmonary artery from the left. This condition is spoken of as *dextrocardia*. The abdominal viscera may be reversed at the same time, the liver being on the left and the spleen on the right side (*situs inversus*). Other abnormalities in the arrangement and origin of the great blood-vessels, such as an undivided truncus arteriosus, are rare.

Stenosis and atresia of the pulmonary artery result from abnormal situation of the septum which divides the truncus. Complete atresia is very rare. Stenosis is one of the commonest developmental defects of the heart, and in some cases is due to fetal myocarditis about the orifice. It may involve the root, the conus, or the trunk of the vessel. The septum of the ventricles is usually defective and the foramen ovale remains patulous. When the stenosis is considerable the pulmonary circulation is often maintained by the persistence of the *ductus arteriosus botalli*, and the right ventricle is greatly hypertrophied.

Stenosis and atresia of the aorta are less frequent than the same conditions affecting the pulmonary artery. They arise from the same cause, and are usually accompanied by the same defects of the septa and patency of the ductus arteriosus. Stenosis of the trunk of the aorta at the isthmus—i. e., at a point between the left subclavian artery and the mouth of the ductus arteriosus—is not infrequent in moderate degree. More rarely there may be almost complete atresia, or the aorta may be entirely wanting at this point. The circulation is maintained by collateral anastomosis of the branches of the subclavian with the descending aorta. In all of these cases hypertrophy of the left ventricle is usually present.

Defects of the ventricular septum may be unaccompanied by other abnormalities; but, as a rule, they are of secondary importance, occurring in cases of abnormality of the pulmonary artery or aorta. The septum may be completely wanting or there may be partial defects, these latter usually lying anteriorly and above, in what is known as the membranous portion or the undefended space.

Defects of the auricular septum are comparatively rare, but a patulous condition of the foramen ovale is one of the most frequent of congenital affections of the heart. It is due to the failure of the valve of the foramen to unite at the edges, as normally occurs some time after birth. Slit-like openings are seen very frequently in postmortem examinations, while more decided patency is occasionally observed without other cardiac abnormalities. This is especially likely to occur when congenital atelectasis or some other pulmonary affection causes continuance of high blood-pressure in the right heart after birth.

Stenosis and atresia of the auriculoventricular orifices are rare congenital conditions, and in the former fetal endocarditis doubtless plays an important part. When there is complete atresia the auricular

septum must remain widely open, and the septum of the ventricle is usually deficient and the ductus botalli patulous.

Patulous Ductus Botalli.—This condition is frequent in cases of stenosis of either the aorta or pulmonary artery, and serves to convey the blood from the patulous artery into that which is obstructed. Like the patulous foramen ovale, it may occur as an independent condition resulting from congenital atelectasis of the lung which leads to the continuance of the fetal conditions of circulation.

Valvular Defects.—Not rarely there may be but two semilunar valves at the aortic or pulmonary orifice, and, on the other hand, four may be observed, the latter being a relatively common condition. Similar numerical abnormalities occur at the auriculoventricular valves. Abnormal length or shortness of the leaflets may also be observed, or the segments may be united, forming a complete ring. The latter condition must not be mistaken for the agglutination of endocarditis. The leaflets may be fenestrated.



Fig. 190.—Congenital cardiac disease, showing peculiar thickness of lips and nose (Eichhorst).



Fig. 191.—Clubbing of the fingers in congenital cardiac disease; from same case as Fig. 190 (Eichhorst).

Pathological Physiology.—Congenital heart diseases occasion serious disturbances of the circulation, leading to overfilling of the venous channels and often abnormal mixture of the arterial and venous blood. In consequence of these conditions blueness or cyanosis is a common symptom, and the terms *congenital cyanosis* and *morbis cæruleus* are applied. The imperfect oxidation of the blood doubtless causes profound effects, but these have not as yet received accurate study. The imperfect circulation causes certain changes in the tissues, notable among which are thickness of the lips and nose, giving rise to a peculiar facial expression (Fig. 190) and “clubbing” of the finger ends (Fig. 191). The blood in congenital cyanosis often contains an excess of red blood-corpuscles. (See Polycythemia.)

CIRCULATORY DISTURBANCES

Thrombosis of the cavities of the heart results from the causes which induce thrombosis elsewhere in the circulatory system. These are, mainly, slowing of the current of blood, some roughness or disease of the endocardial lining, and diseased conditions of the blood itself, which render it more liable to coagulation. Slowing of the circulation is the most frequent cause of intracardiac thrombosis, and leads to the formation of the clots found postmortem in cases of gradual death. If the circulation has been slow for a considerable length of time, there may be found more or less grayish or white thrombi in the appendages of the auricles or in the ventricles between the muscular trabeculæ, especially near the apex. The formation of these is explained by the gradual slowing of the current of blood, which leads to the deposit of the leukocytes and blood-plaques upon the endocardium and the deposition of fibrin. The color may be almost completely white; but if the current is almost stagnated, admixture of red corpuscles occurs and pinkish or quite red clots (*currant-jelly clots*) are formed. Of this latter sort are the thrombi formed in the heart during the agonal period and postmortem. They are further distinguished from the thrombi formed *intra vitam* by the fact that they are not closely attached to the endocardium and between the trabecular muscles.

Among the diseases in which the circulation is prone to be sluggish, and which are frequently accompanied by cardiac thrombosis, pneumonia, tuberculosis of the lungs, the asthenic fevers, and diseases of the muscle of the heart may be named. Dilatation of the chambers of the heart and cardiac aneurysm lead to thrombosis by their effect upon the rapidity of the circulation either in the general heart-cavity in the first, or in the aneurysmal dilatation in the second. Among the endocardial lesions which occasion thrombosis the most important is acute endocarditis. In this condition there is habitually deposited upon the affected part of the valves or mural endocardium a capping of fibrin deposited from the blood passing over the diseased area. In chronic endocarditis, especially when there are irregular calcareous deposits rendering the surface rough and uneven, considerable thrombotic deposit may occur.

Pathological Anatomy.—Cardiac thrombi, formed some time before death, usually appear as deposits upon the heart wall of a yellowish or whitish color and rather firmly attached between the muscular trabeculæ. Occasionally they have a stratified appearance, due to the fact that the circulation varied in rapidity during the formation of the thrombi. Secondary changes are not rare, the most striking being softening of the fibrinous mass in places, with the formation of cyst-like



Fig. 192.—Thrombosis in cardiac chambers, showing cyst-like structure (Orth).

cavities varying in size from a split pea to a cherry (Fig. 192). Sometimes thrombi project from the endocardial surface in a polypoid form, and these may present the appearance of fibroid tumors. A curious form occurs in the auricles, the thrombus presenting itself as a round mass attached to the endocardium by fine pedicles or lying entirely free (*ball-thrombi*, *globular thrombi*).

Lesions in Other Organs.—Thrombosis of the heart may occasion serious disturbance of the circulation by weakening the heart muscle or by obstructing the valvular orifices. The latter is especially common in the case of the globular thrombi or the polypoid thrombi of the auricles. Passive congestion of the various organs and the secondary changes due to this condition follow. Thrombosis may lead to another and more serious danger, that of embolism. When portions of the thrombus are broken off they are carried into the circulation and lodge in the small arteries of the spleen, the kidney, the brain, the lungs, or elsewhere, causing infarctions, or, in case micro-organisms be present in the original thrombus, metastatic abscesses and pyemia.

Thrombosis and Embolism of the Coronary Artery.—The former condition is much the more common, as the coronary arteries are frequently the seat of advanced atheromatous narrowing and roughening, which predispose strongly to thrombosis; and, on the other hand, the mouths of the coronary arteries are so placed that emboli are unlikely to enter. The lodgment of an embolus seriously compromises the heart's action, as has been shown experimentally in animals, and marked pathological change is, therefore, unlikely to occur before death ensues. When a partially obstructing embolus lodges or a thrombus is formed there results almost complete anemia of the area supplied by the artery affected, and, in consequence, an anemic infarct. The muscle-fibers of the affected area become hyaline or granular, and do not take the stain when subjected to ordinary histological examination. To the naked eye the diseased portion presents itself as a white, and later as a yellowish, area of softening, and the condition is spoken of as *myomalacia cordis*. It is found most frequently in the anterior or posterior wall of the left ventricle, near the apex, from the fact that the descending branch of the left coronary artery is the most commonly occluded vessel. Next in frequency to these points the anterior portion of the septum is found to be affected. Small areas may heal by absorption of the degenerated tissue, and by infiltration and proliferation of connective tissue. In this manner a scar is formed which may remain, or may subsequently lead to aneurysmal dilatation. On the other hand, rupture of the heart may be occasioned either with or without the formation of an acute aneurysmal dilatation at the degenerated area.

DISEASES OF THE ENDOCARDIUM

The endocardium, both mural and valvular, is subject to edema and hemorrhage either independently or as forerunners of inflammation. Hematomata have been seen in the valves. Fatty, mucoid, hyaline, amyloid, and calcareous changes have been seen.

INFLAMMATION

Inflammation of the endocardium, or endocarditis, may be acute or chronic; the latter is in most cases merely a continuation of the former.

Acute endocarditis affects the endocardium of the valves in the great majority of cases, but it is sometimes found in the endocardium of the cavities of the heart, when it is spoken of as *mural endocarditis*.

Etiology.—Endocarditis is practically always a secondary process, and is in nearly all, if not all, cases due to the action of micro-organisms. Cold and traumatism, upon which the older writers insisted as causal factors, act merely as predisposing causes. Endocarditis occurs most frequently in association with acute articular rheumatism. Next to this cause, scarlet fever, pneumonia, and various forms of sepsis are most important, but in any case of suppurative or infectious disease endocarditis is a possible complication. Even the seemingly mild infections like tonsillitis may occasion endocarditis. It occurs at times also in Bright's disease and in conditions of great malnutrition, such as carcinoma and certain nervous affections. These cases have been cited as opposing the view that endocarditis is always infectious and due to micro-organisms. It may be that toxic substances resulting from improper metabolism act upon the endocardium as do micro-organisms, or that portions of the endocardium suffer degeneration as a result of depressed nutrition, but it is more probable that terminal or intercurrent infection from some hidden source may occur in these chronic diseases, with resulting endocarditis.

As to the micro-organisms themselves, the most important are the *Staphylococcus pyogenes aureus*, the *Streptococcus pyogenes*, and the *Diplococcus pneumoniae*. A special form of streptococcus distinguished by certain rather marked cultural features, the *Streptococcus viridans*, has in recent years been found especially frequent in certain cases of sub-acute endocarditis or recurrent endocarditis. There are many forms which have been less frequently detected. Among those reported are the *Staphylococcus pyogenes albus*, the *Micrococcus endocarditidis capsulatus* and *rugatus*, the *Bacillus endocarditidis griseus* and *capsulatus*, *B. pyogenes fœtidus*, *B. coli communis*, the *B. diphtheriae*, the *B. aerogenes capsulatus* (Welch), or the bacillus of Achalme, and the bacillus of typhoid fever. The tubercle bacillus has been found in a few cases, but it is generally believed that its presence is explained as a secondary deposit rather than as the cause of the endocarditis. The gonococcus has been found capable of causing endocarditis.

The bacteria causing the valvular inflammation settle upon the endothelium from the blood-stream in all probability, but an infection through the base of the valve cannot be entirely excluded. When, by reason of toxins circulating in the blood, or forceful impact of the leaflets, due to overaction of the heart, or disturbed lymph-supply of the valve stalk, the endothelium swells, it forms a favorable settling place for bacteria passing over the valve in the blood-stream. When the bacteria have become attached they are taken up by the phagocyte power of the

endothelium. Over such a section of turgid endocardium strands of coagulum may appear; this adds another factor favoring bacterial attraction by showing the current at that point.

In all cases of general infection there is a myocarditis and, as the blood- and lymph-supply of the valves are scanty, edematous swelling of the free part of the leaflet may arise. From a lesion in the muscle near a valve base it is possible that bacteria may spread into the valve stalk.

Valves are not supplied with blood-vessels, but it has been suggested that mild inflammations in early life leave some vascularized scar tissue in which capillaries may serve as avenues to the distal end of the valves, where lesions will occur upon a subsequent infection.

Pathological Anatomy.—It is customary to distinguish two varieties: a *simple* or *verrucose*, or benign endocarditis; and an *ulcerative*, *septic*, *mycotic*, *diphtheritic*, or malignant form; but it seems unnecessary at the present time to maintain strictly such a distinction. The cases

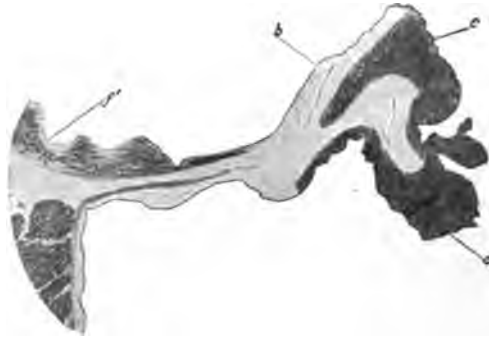


Fig. 193.—Section through a segment of the aortic valve and adjacent parts of the aorta and heart, showing vegetations on the aortic valve (magnified): *b*, Aortic valve segment; *c*, *c'*, vegetations; *f*, calcareous particles in the base of the aortic valve (Bramwell).

vary in anatomical appearance and in malignancy, but there is no essential difference and no sharp dividing line.

The most common seats, in order of frequency, are the mitral valve, the aortic valve, the pulmonary valve, and the endocardium of the left ventricle, the left auricle, and the right ventricle. The part of the valve first involved is a line running across the leaflet at about a distance of 2 mm. from the free edge. It is along this line that the valves impinge in closing, and it is probable that the mechanical injury sustained predisposes to endocarditis. In the cavities the lesions are frequently found upon the *chordæ tendineæ*, and of the parts of the mural endocardium proper most apt to be affected may be mentioned the portion of the left ventricle near to the septum and the aortic valves, and the endocardium of the left auricle on the posterior and outer wall above the posterior mitral leaflet.

The first appearance of endocarditis is that of an area of opacity or slight roughness extending in a line across the valve or involving the endocardium elsewhere. Later, small nodular elevations, not unlike

a row of small beads, may form; and finally there is a distinct, irregular, and wart-like fibrinous elevation (Fig. 193). To cases of this character the name *verrucose endocarditis* (Fig. 194) has been given; or, from the usually benign character, the name *simple endocarditis*; or, from its most frequent cause, *rheumatic endocarditis*. In other cases the mass of fibrinous deposit is more abundant and more irregular, while in still others the deposit of fibrin does not take place, or, if so, is soon detached, while necrotic changes occur in the endocardium, leading to the formation of irregular ulcers. Secondary deposits of fibrin may cover an ulcer after its formation, or its edges may be heaped with fibrin; and not rarely the active necrotic process in the endocardium is not visible until the fibrinous coating, which is usually considerable in such cases, is removed.



Fig. 194.—Acute vegetative (verrucose) endocarditis.

These forms of endocarditis are those that have been termed *malignant*, *diphtheritic*, *septic*, *mycotic*, or *ulcerative*. They are especially frequent after puerperal sepsis or other septic diseases and in pneumonia, but there is no well-established dividing line between the benign cases and the severe cases, either in etiology, in morbid anatomy, or in the clinical course and termination, so that we prefer to regard them as varying grades of the same general process.

Microscopically, the endocardium beneath the coat of fibrin shows desquamation of the endothelial cells, with frequently some hyaline degeneration or coagulation necrosis. Below this there are round-cell infiltration and, as the process continues, proliferation of fibroblastic cells. The fibrinous covering of the valve itself consists of flakes or

granular masses, or a fibrillar network. By the proper staining methods masses of bacteria may frequently be demonstrated in the superficial layers of the endocardium, in the fibrinous deposit, and usually at the bases of the leaflets or in the muscle.

The simple differs from the malignant forms of endocarditis merely in the lesser activity of the necrotic changes in the endothelium and the greater prominence of reparative processes (round-cell infiltration, proliferation of connective tissue).

Associated with endocarditis will always be found some degree of myocarditis. The myocarditis is usually degenerative, but in the severe septic cases is infiltrative and necrotizing. Such myocarditides are almost always replaced by cicatrization, except in rheumatic myocarditis (*q. v.*).

Results.—Simple endocarditis may be healed by the gradual absorption or breaking off of the fibrinous deposit and its dissemination

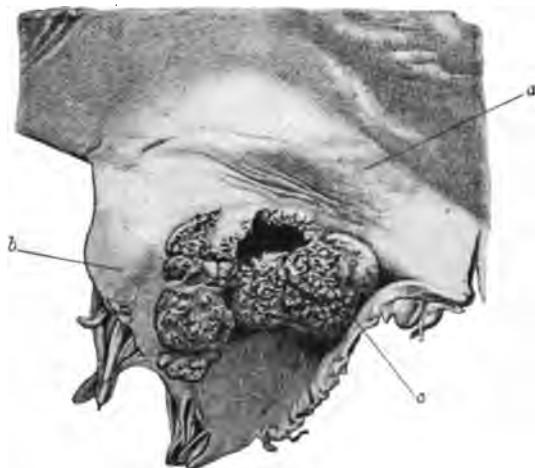


Fig. 195.—Aneurysm of the mitral valve, with rupture of the valve-cusp, seen from the auricular surface: *a*, Wall of left auricle; *b*, anterior segment of the mitral valve, the chordæ tendineæ have been cut short; *c*, aneurysm with triangular opening (Bramwell).

in the circulation, with coincident thickening of the endocardium at the point of disease by the formation of fibroblastic cells and sclerotic connective tissue. When the process is very limited; and especially when the mural endocardium is affected, merely a white spot of thickening on the endocardium results. When the process is deep there may be decided distortion by contraction of the new-formed connective tissue. When the deposit of fibrin is large it frequently undergoes calcification, and remains as an irregular, calcareous mass attached to the valve. In the severer or malignant cases destruction of an entire valve or of one of the chordæ tendineæ may occur. When one of the layers of the valve alone is penetrated acute valvular aneurysm may be formed by a pouching of the other layer of the valve (Fig. 195).

Mural endocarditis of malignant type may lead to myocarditis

of a purulent character, and may even penetrate to the pericardium and set up a purulent pericarditis.

Lesions in Other Organs.—The most serious danger of endocarditis is embolism. Small fragments of the fibrinous deposits are liable to be carried off into the peripheral circulation, and in ulcerative cases fragments of the valves themselves may be so conveyed. They are prone to lodge in the arteries of the spleen, kidneys, and brain, forming hemorrhagic infarcts or metastatic abscesses, according to the non-infective or infective character of the embolus.

Subacute or chronic malignant or recurrent endocarditis is that form in which the pathological change in the valve is not of a rapidly progressive nature, but is often sluggish or chronic in its pathological and clinical behavior. The term "recurrent" has been used to indicate that cases of old valvular lesions are especially prone to this type of reinfection. There is commonly a bacteremia, the most common organism found being a streptococcus similar to both the pyogenic streptococcus and the pneumococcus, called the *Streptococcus viridans*. We have discussed the nature of the infection under the general subject of remittent infections; the reason for the persistence of the organism in the body for so long a time will be found by consulting the text upon *fixed* or *fast* bacterial strains. The pathological lesions are those of low-grade vegetative endocarditis, with the evidences of continued congestion of the lymphatic tissues and bone-marrow. Nephritis may arise. The termination may be gradual exhaustion, an acute exacerbation and death, or transition to a cicatrizing endocarditis.

Chronic endocarditis usually affects the valves of the heart and leads to the distortion of the valves constituting chronic valvular heart disease. Clinically, there are signs of disturbances, and eventually more or less complete failure of the circulation.

Etiology.—Chronic endocarditis may be merely the continuation of acute endocarditis, or it may occur as an insidious process, chronic from the outset. In the former group of cases the causes are, of course, those of acute endocarditis, and it is particularly the rheumatic form that is likely to pass on to a chronic condition. The severer grades of acute endocarditis, or those commonly spoken of as malignant endocarditis, are usually fatal, though occasionally they may terminate by reparative overgrowth of fibrous tissue. The group of cases in which the disease is chronic from the start has much in common with arteriosclerosis and atheroma, as far as etiology is concerned. They may be toxic in their origin. These cases occur more frequently in persons of advanced years and in those whose occupation has been laborious. Chronic alcoholism, gout, lead-poisoning, syphilis, and diabetes are among the recognized causes. Not rarely the endocardial disease is secondary to the arteriosclerosis, and it may be directly due to it, resulting from the constant elevation of blood-pressure due to that disease. Laborious occupations act in a similar manner.

Pathological Anatomy.—In brief, the changes that occur in the endocardium are overgrowth of fibrous tissue, causing thickening with

subsequent contraction and distortion of the valves. The chordæ tendinæ are frequently involved and become converted into sclerotic cords of a whitish color, and less frequently white elevations are seen upon the mural endocardium.

Microscopically, there are found the characteristic appearances of new-formed connective tissue, with occasionally, in the earlier states, the appearances of granulation tissue. New-formed blood-vessels may be found within this tissue, though frequently these are degenerated (hyaline and obliterated). Subsequently other degenerations take place. The area of thickening becomes more translucent and hyaline, then opaque and soft; coagulation necrosis and fatty degeneration take place, and there may thus be formed beneath the endocardial surface a lesion somewhat resembling a minute abscess. This may rupture upon the endocardial surface, forming a so-called atheromatous ulcer, upon which fibrinous deposits may collect; or it may be slowly inspissated and converted into a calcareous patch. In cases in which acute endocarditis with thrombotic deposits passes into chronic endocarditis the fibrinous masses of the surface may be rendered calcareous at the same time that the sclerotic processes are taking place in the valve. Subsequently the same degenerative changes and calcification may occur in the tissue of the valve itself as are seen in the atheromatous form of the disease. In the late stages it is often quite impossible to determine whether the case began as an acute endocarditis, or whether it was chronic from the first.

The segments of the valves are frequently greatly shortened and rounded, so that they become mere stumps, or they may be curled upon themselves or drawn back and firmly adherent to the wall of the aorta, pulmonary artery, or the ventricular cavity. The individual segments may be agglutinated and united as a ring or diaphragm projecting from the valvular insertion.

The valvular function is interfered with in two ways: first, obstruction may be offered to the outflow of blood by the rigid projecting valves and contracted orifice, a condition to which the term *stenosis* is applied; or, on the other hand, the valves may be so distorted, shortened, or drawn backward that they are no longer able to close, and *insufficiency* results. The semilunar valves are particularly prone to be shortened, thickened, and recurved, and insufficiency is, therefore, most likely to occur. The mitral valve is frequently thickened and converted into a funnel-like formation by agglutination of the edges of the anterior with those of the posterior segment. There may thus be merely a slit-like orifice (button-hole mitral), which occasions great obstruction to the outflow of blood from the auricle. Somewhat similar changes are met with at the tricuspid valve. The pulmonary valve is rarely affected in later life, but is sometimes the seat of fetal endocarditis, leading to permanent changes.

Resulting Changes in the Heart.—The valvular defects can be overcome in only one way—by increase of the power of the heart muscle. Hypertrophy is, therefore, the natural result. This affects

first the cavity upon which excessive work falls as the result of the regurgitation of blood in cases of insufficiency, or as the result of the excessive strain placed upon the heart wall to force the blood through the narrowed orifice in stenosis. The amount of hypertrophy varies with the condition of the general health of the individual and with the seriousness of the heart lesion itself. When the general health is good there is apt to be commensurately adequate hypertrophy, and when the lesion is not of sufficient gravity to interfere with the circulation in the coronary arteries, and the heart is, therefore, constantly supplied with a sufficiency of blood, hypertrophy is well maintained. Eventually, as the result of continued overwork and of continuously increasing embarrassment of the circulation or of intercurrent diseases, the heart muscle suffers fatty or fibroid degeneration, the cavities dilate, and the circulation fails.

Changes in Other Organs.—The passive congestions resulting from failure of the muscle of the heart are often extreme, and may lead to profound changes in various organs, notably the lungs, liver, and kidneys. These are discussed in the appropriate sections. Embolism is a not infrequent accident in chronic endocarditis, the emboli being parts of the valvular deposits or parts of thrombi in the cavities of the heart.

Pathological Physiology.—Endocarditis, acute and chronic, leads to various disturbances of the circulation and of the general health. In acute endocarditis the lesions may become the center of dissemination of infectious material, and the disease may run its course with all the manifestations of an obscure septicemia. This is particularly true of the cases usually designated as malignant. Serious disturbance of the heart action occurring in acute cases is sometimes difficult to explain. The lesions upon the valves may be seemingly very insignificant, and yet the heart may be very irregular in action and exceedingly weak. In part this may be reflex and in part it is probably the result of associated disease of the myocardium. Some investigations, made according to modern methods, have shown the heart muscle implicated more often than has been suspected. Acute myocarditis and diseases of the blood-vessels of the myocardium (thrombosis) have been discovered.

Chronic endocarditis (valvular disease) occasions more or less profound mechanical disorders of the circulation. The severity of these depend upon the condition of the heart muscle more than upon the severity of the valvular lesion. There is always a tendency to compensatory hypertrophy of the heart muscle, and for a time this may suffice to avert serious disturbances; but with hypertrophy there is always some degenerative change (fibrous myocarditis and, later, fatty degeneration), as a result of which the cardiac power eventually fails, and symptoms of venous congestion develop. The degree of hypertrophy and of degeneration depends upon the nature and severity of the valvular lesion, upon the age and general condition of the individual, and upon associated local conditions, such as disease of the coronary artery.

When compensation fails the various organs of the body suffer congestion. The lungs are first affected in disease of the left heart (mitral and aortic disease). The capillaries of the pulmonary alveoli become overfull, and encroach upon the lumen of the alveoli, or by elongation stretch the alveolar walls and render them inelastic. In either case proper respiration is prevented—a condition which is further aided by the retarded pulmonary circulation. As a result of these conditions, dyspnea (cardiac asthma), cough, and expectoration develop. In extreme cases edematous exudation takes place, and in long-continued cases cyanotic induration of the lung occurs. In such instances there may be continuous cough and respiratory insufficiency.

When the right heart fails, the liver, spleen, gastro-intestinal mucosa, the kidneys, and the peripheral circulation suffer congestion. The liver may become greatly engorged, and in certain cases (tricuspid regurgitation) actually pulsates with each ventricular systole. The swollen liver cells and the engorged vessels cause obstruction of the biliary capillaries, and consequently produce jaundice. To some extent this may be due to associated congestion of the biliary channels. Congestion of the gastro-intestinal mucosa may occasion various forms of gastric or intestinal derangement.

Metabolic disturbances of various sorts may occur in consequence of the imperfect circulation. The respiratory exchange of gases, in some cases at least, is reduced, though the degree of cyanosis cannot be taken as an index of the reduced oxidation. In man cyanosis is dependent upon stagnation of circulation rather than reduced oxidation. The products of metabolism excreted in the urine may indicate the reduction in oxygen in the tissues. The metabolic consumption of the proteins of the body seems to be increased, but the explanation of this fact has not yet been satisfactorily determined. Some regard it as a consequence of molecular necrosis due to insufficiency of the supply of oxygen. The excretion of nitrogenous elements may, however, be reduced when transudates are forming. This is due to the storing up of metabolic products in the transudates. The urine may present albumin as a result of chronic congestion and secondary renal disease; the hepatic functions are disturbed by congestion and jaundice may result; and in the more severe instances hydrobilirinuria occurs. The condition of the blood is of special interest. During periods of failing compensation the concentration of the blood is increased or normal, and the number of blood-corpuscles may be excessive. In part, at least, these conditions are explained by the assumption that the corpuscles are retained in the peripheral parts of the circulation in greater measure than the fluid elements (see Polycythemia). When the cardiac compensation is well maintained some anemia may be apparent, especially in cases of aortic disease.

Disturbance of the rate or rhythm of the heart is not infrequent. The rate is usually more rapid, but in aortic stenosis it may be slow. This is in effect a conservative process, as it enables the ventricle to discharge its contents through the narrowed orifice. Arrhythmia is gener-

ally proportioned to the grade of degeneration of the muscle of the heart. and is especially marked in cases in which the walls of the auricles are involved. The attempt to connect disorders of rhythm with disease of the intracardiac nervous mechanism has thus far failed of demonstration. On the other hand, the relation of myocardial disease to arrhythmias has become increasingly evident. Increased irritability of the heart muscle in certain stages of myocardial disease readily explains some of the cases of extrasystolic irregularity. Lesions of the bundle of His may occasion partial or complete dissociation of the auricular and ventricular contractions (partial or complete "heart-block"). Various other types of arrhythmia may also be explained by myocardial disease.

MYOCARDIUM

CIRCULATORY DISTURBANCES

Anemia of the heart muscle may be part of a general anemia. It may occur in cases of narrowing or obstruction of the coronary arteries, and it may be the result of the pressure of pericardial effusions. When long continued it leads to fatty degeneration of the heart, but is itself of little consequence.

Hyperemia of the heart muscle may occur when there is obstruction to the return of the blood to the right heart through its venous channels. It may be part of a general hyperemia in a failing compensation of valvular or muscular diseases of the heart. The heart muscle assumes a dark-red color, and the veins are seen under the epicardium as dilated bluish vessels.

Hemorrhages in the heart muscle may result from obstruction of the coronary arteries, when the hemorrhage assumes the form of an infarct. There may also be hemorrhages in cases of intense myocarditis or surrounding abscesses of the heart muscle, and finally points or streaks of hemorrhagic infiltration may be seen between the muscle-fibers in persons who have died from some form of hemorrhagic diathesis, from sepsis, or from various intoxicants.

DEGENERATIONS

Parenchymatous degeneration, or cloudy swelling of the heart, was designated by Virchow as parenchymatous myocarditis. It is essentially a degenerative process and should be so described, though it forms a not inconsiderable part of the pathological changes occurring in the heart in acute myocarditis.

Etiology.—The immediate cause is infection. It is met with in the course of diphtheria, typhoid fever, scarlet fever, rheumatism, and other infections. It may be that elevation of the temperature alone suffices to bring it about, and in these cases no doubt abnormal substances resulting from disordered metabolism are the direct toxic agents, but, as a rule, it is the specific toxin of the infections that occa-

sions the myocardial disease. Localized parenchymatous degeneration may be found in the heart-fibers adjacent to areas of endocarditis or pericarditis, and doubtless the same etiological factors are at work in this as in more generalized instances.

Pathological Anatomy.—The changes are more marked in the left ventricle than elsewhere, though any part of the heart may be affected. As a rule, parenchymatous degeneration occurs as a diffuse process, but there may be only limited areas here and there. The myocardium becomes pale in color; it is softer than normal, the heart walls are usually flabby, and the cavities somewhat dilated. Microscopically, the fibers are found to be filled with fine granules of albuminoid nature, which may completely obscure the striations and even the nuclei, but which may be cleared up by the addition of acetic acid. Multiplication of the nuclei and round-cell infiltration of the intermuscular connective tissue may be observed, but these are inflammatory changes rather than degenerative, and are not, therefore, strictly a part of the disease in question. Parenchymatous degeneration may be complicated by a form of hyaline degeneration, the affected fibers becoming converted into cylinders of waxy appearance. When cloudy swelling persists, fatty degeneration is usually the terminal change.

Amyloid infiltration results from the causes which induce amyloid disease in other organs. It is not infrequently found in minute areas here and there, but only rarely has it been seen as a widespread process affecting the connective tissue between the muscle-fibers and beneath the endocardium and pericardium. In such cases the same wax-like appearance is seen as in the liver or spleen, and the characteristic reaction with iodine may be demonstrated.

Hyaline degeneration is sometimes associated with amyloid, and gives rise to a glassy or waxy transformation of the connective tissue. It is usually seen in small areas, but may be quite widespread. Zenker described a form of hyaline disease (vitreous degeneration) of the muscle-fibers themselves as occurring in typhoid and other infectious fevers, and affecting the heart muscle as well as the muscles of the abdominal wall. This is usually associated with parenchymatous degeneration and occurs in limited areas. Microscopically, there may be seen small hyaline masses or globular areas embedded in the muscle-fiber, the rest of the fiber showing the appearances of cloudy swelling.

Fatty infiltration, or *obesitas cordis*, is but an increase of the normal condition. In the normal heart there is a certain amount of fatty deposit beneath the epicardium, especially in the furrows and along the lines of the blood-vessels. In disease this may become enormously increased and there may be penetration of the adipose tissue into the wall of the heart between the muscle-fibers, sometimes as far as the sub-endocardial fibrous layer.

Etiology.—The causes are those which induce general obesity. Thus, it may be the consequence of a hereditary tendency or sedentary habits, with overeating and drinking; it is more common in advanced years than in early life. Very frequently it is met with in women who

have grown stout at the menopause; sometimes, however, considerable deposit about the heart may occur in persons otherwise presenting no tendency to fatness.

Pathological Anatomy.—The adipose tissue beneath the visceral pericardium may be slightly increased in amount, or the heart may be embedded within an enormous deposit of fat, which may involve not alone the epicardium, but the parietal layer and the mediastinum as well. On section through the heart wall, trabeculæ of adipose tissue may be seen passing through the heart's substance, and sometimes deposits may be seen as a uniform infiltration beneath the endocardium, or as localized deposits projecting into the heart cavity. Microscopically, fatty infiltration presents the ordinary appearances of adipose cells lying between the heart muscle-fibers (Fig. 196). The muscle-fibers themselves are not involved; but may become atrophic

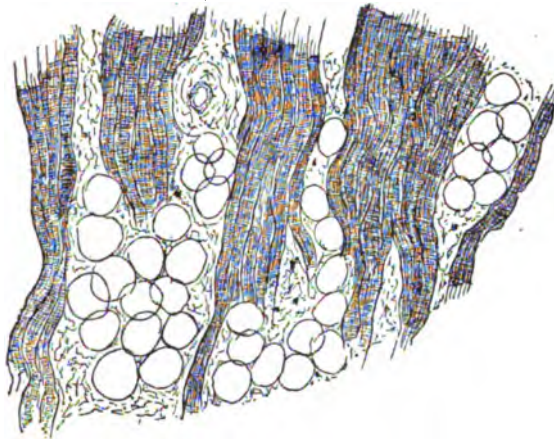


Fig. 196.—Fatty infiltration of the heart, from a section through the wall of the right auricle (Bramwell).

from pressure, and in such instances present a more yellowish or brownish color than normal, and microscopically show an abundance of granules. In other cases pronounced fatty degeneration is seen in the muscle-fibers.

Results.—Weakening of the heart muscle must necessarily result from the mechanical impediment imposed upon it. Circulatory disturbances are, therefore, met with, as in valvular disease or fatty degeneration. Occasionally rupture of the heart occurs, due to the atrophic condition of the muscle proper and a want of resisting power of the infiltrating adipose tissue. It is especially prone to occur when the disease is localized.

Fatty degeneration affects the muscle-fibers themselves.

Etiology.—Fatty degeneration results from malnutrition or from toxic agencies. The most frequent cause is anemia, either local or general. Local anemia is due to sclerosis and narrowing of the coronary

arteries; or it may be the consequence of improper circulation in the coronary vessels attending the final stages of valvular disease of the heart. Fatty degeneration is, therefore, a terminal condition in arterial sclerosis affecting the coronary vessels and in valvular disease. The remote or antecedent causes are those which bring about arteriosclerosis. We find it, therefore, in elderly persons of the male sex who have had syphilis, who have used alcohol excessively, or have gout or chronic Bright's disease. The fatty degeneration of the heart resulting from general anemia is most typically seen in pernicious anemia, in which the most extreme grades of fatty disease are sometimes witnessed. Of the cases which are due to toxic agents, we may distinguish those resulting from specific infections and those occurring in various chemical intoxications. In the specific fevers, in which intense parenchymatous degeneration occurs, and among these diphtheria is most prominent, fatty degeneration is sometimes the terminal condition. Among the external poisons capable of producing the disease phosphorus and arsenic are important.

Pathological Anatomy.—Fatty degeneration may be a localized or a diffuse process. As a rule, a considerable portion of the heart is affected,

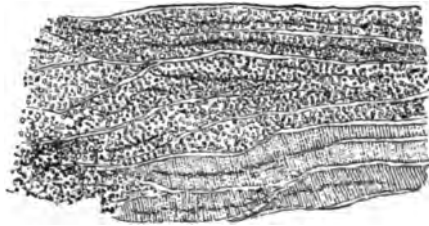


Fig. 197.—Fatty degeneration of the heart in a case of pernicious anemia; some of the fibers in the lower part of the illustration are normal (Birch-Hirschfeld).

but only isolated fibers or groups of fibers are involved. There results a somewhat speckled or mottled condition (tigation), which is especially visible beneath the endocardium. Streaks or lines of a yellowish or whitish color alternate with the darker portions of normal muscle. When the process is uniform the entire muscle assumes a yellowish hue. It is softer than normal, the cavities tend to dilate, and the walls may be considerably thinner than normal.

Microscopically, the muscle-fibers are found to be filled with small granules of a dark color or with small droplets of high refractive power (Fig. 197). These may completely obscure the nucleus, or they may be arranged in groups at the poles of the nucleus. Sometimes distinct vacuolization of the fibers is seen, especially in cases in which fibroid myocarditis accompanies the fatty change. The nature of the granules and droplets within the fibers is well demonstrated by treating the section with osmic acid, when the fat-droplets become intensely black.

Associated Conditions.—In cases of coronary sclerosis, or valvular heart disease with failure of compensation, fatty degeneration is rarely

the sole pathological condition. As a rule, fibroid myocarditis accompanies it, and the latter may be the more extensive and important condition of the two. Fatty infiltration is often met with as an associated condition, and may be the direct cause of the degeneration by the pressure exerted upon heart muscle-fibers by the infiltrating fat. Rupture of the heart may occur in cases in which fatty degeneration affects localized areas, as is often the case near the apex of the heart.

Segmentation of the Fibers.—This is an interesting condition occasionally observed, especially in cases in which sudden death has taken place. It consists in a transverse splitting of the fibers, by which they are converted into columns of varying length separated by transverse fissures (Fig. 198). It has been described under the name of *état ségmentaire* or *myocardite ségmentaire* by French writers. A considerable discussion as to its significance has arisen, some holding that



Fig. 198.—Marked general segmentation with great diastasis of the pieces; $\times 120$ (from the *American Journal of the Medical Sciences*) (Hektoen).

it is a condition of clinical as well as of pathological importance; others, that it occurs during the death-agony or postmortem. Whether the latter statement be true or not, the segmentation seems to indicate an abnormal fragility of the fibers and in particular of the cement-substance, though it may not be demonstrable by our present means of examination. Some observers maintain that it occurs when there has been excessive dilatation of the heart just antemortem. This fragility may be due to digestive action of bacteria or bacterial products, as has been suggested. Some investigations seem to indicate that segmentation is purely artificial, and brought about by the imperfect adjustment of the knife in cutting.

Degeneration of the intracardiac ganglia has been noted by a number of observers in myocarditis and in cases of angina pectoris without gross cardiac alteration. The changes observed are swelling or granular,

fatty and hyaline degeneration of the ganglion-cells, and infiltration with round cells and sclerotic formation between the nerve-cells. The importance of these changes has not been determined.

Pathological Physiology.—The functional disorders in degenerations of the myocardium may be due to the direct injury of the fibers, or to disturbances of the nervous mechanism of the heart. The latter seems to be the case in instances in which marked cardiac irregularity, or arrhythmia, occurs. The disease of the fibers explains the weakness of the heart's action; and this is especially marked in cases of fatty and fibroid disease in which the circulation through the coronary arteries is insufficient. Recent investigations have shown that fatty degeneration of the heart muscle in itself causes much less cardiac weakness than has generally been supposed. Sometimes the heart is arrested and sudden death occurs in cases of myocardial degeneration due to infectious fevers (diphtheria). This was formerly ascribed to heart-clots, but is now recognized as a form of sudden and complete asystole due to the myocardial disease or to associated nervous disorders, organic (in the intracardiac ganglia or in the cardiac nerves) or reflex. The disturbances of the general circulation in myocardial disease and their results are similar to those met with in valvular disease. (See also *Pathological Physiology of Fibroid Degeneration of the Heart.*)

The result of physiological investigations has been to give greater importance to the integrity of the muscle-fibers than to that of any intracardiac nervous mechanism in the maintenance of regular rhythmic action of the heart. It has been found that the muscle-cells have the properties of stimulability, conductivity, and contractility. The impulse to contraction originates near the opening of the superior vena cava, and is conducted through certain muscle-fibers (conductivity) and received by the fibers of the auricle and the ventricle (stimulability), which are thus made to contract (contractility) in an orderly fashion. If any one of the properties is disordered, arrhythmia or altered rates of contraction result. In passing from the auricle to the ventricle the impulse traverses a narrow band of muscle (atrioventricular bundle of His), the only muscular connection; and both physiological experiment and autopsy findings in cases of Stokes-Adams' disease have shown that destruction of His' bundle causes independent contraction of the auricles and ventricles, the former beating as frequently as 80 or 100, the latter between 20 and 30. The term "heart-block" has been given to this condition by physiologists.

INFLAMMATION

Inflammation of the heart muscle, or myocarditis, may be either acute or chronic, diffuse or circumscribed.

Acute myocarditis was designated "carditis" by the older writers, though the same term was applied to endocardial and pericardial inflammations as well. It may be circumscribed or diffuse, the former appearing most frequently in the form of abscesses of the heart muscle.

Acute circumscribed myocarditis, or abscess of the heart, may occur in connection with penetrating endocardial lesions or in association with pericarditis. More frequently the infection takes place through the coronary circulation, and the metastatic abscesses of the heart are but a part of a general pyemic disease (Fig. 199) such as occurs in puerperal sepsis, in osteomyelitis, and other intensely septic diseases, but particularly in malignant endocarditis.

Pathological Anatomy.—When the infectious emboli are large, a single abscess or a few abscesses result, while in cases of finely disseminated infectious particles the heart substance may be studded with innumerable suppurating points. These are more common in the left ventricle and in the anterior wall than elsewhere. At first the lesion may present itself as a minute, hemorrhagic, or necrotic area, but soon the focus softens and forms a purulent collection. In size the abscesses vary from the merest points to cavities the size of a cherry, and as much

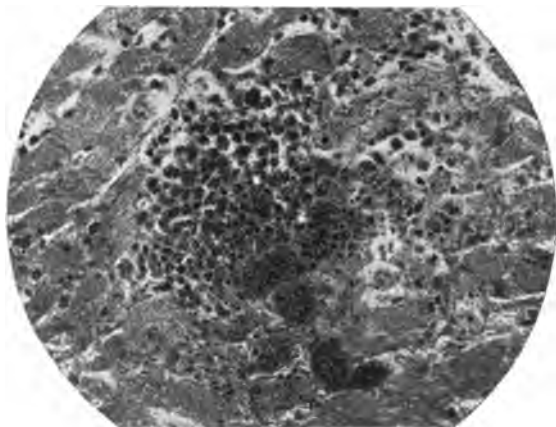


Fig. 199.—Embolic abscess of the myocardium.

as an ounce of pus has been removed from a single cavity. Perforation may take place into the heart itself, and acute cardiac aneurysm or even rupture of the heart may ensue. On the other hand, the abscess may discharge into the pericardial sac, or without such rupture may set up purulent pericarditis. Occasionally the pus becomes inspissated and fibrous overgrowth causes its complete encapsulation, or finally, the area may be rendered calcareous. Such terminations, however, are rare, the patient usually perishing of the pyemic process, as a part of which the abscesses in the heart occur.

In suppurative myocarditis occurring from extension in consequence of malignant endocarditis communicating sinuses may be established between the chambers of the heart.

A non-suppurating form of interstitial myocarditis may occur, and Aschoff has called attention to such a process in rheumatic conditions associated with endocarditis. A similar lesion has been found in the

heart in chorea. There is a leukocytic infiltrate and local cell hyperplasia, sometimes in nodular form, following the blood-vessels. There may be a small amount of fibrin. This lesion occurs most commonly in the left ventricular wall. It may be removed without leaving a trace, or a small fibrotic patch may remain.

These bodies are not producible in experimental animals by injection of the cocci which can cause endocarditis and are said to cause rheumatism.

Acute diffuse myocarditis occurs in various forms of infectious fevers. It was first recognized in typhoid fever, but is more common in diphtheria and scarlet fever, and is met with in acute rheumatism, puerperal septicemia, and various other infections. It is most likely that the toxins of the infectious diseases named are the immediate causes, and not the specific bacteria themselves. The process may be entirely diffuse, but in most cases the left ventricle is more seriously involved than other parts, and often there are merely localized areas of myocarditis scattered about in various parts of the ventricular wall.

Pathological Anatomy.—The affected heart muscle is soft and often distinctly friable. In the earlier stages there may be spots of hemorrhagic infiltration, but, as a rule, the color is rather lighter than that of the normal organ. It may be noticeable that the bundles of fibers easily separate from one another. The cavities of the heart are frequently dilated, particularly the left ventricle.

Microscopically, the important changes are diffuse infiltration of round cells in the connective tissue between the muscle-fibers (Fig. 200), and proliferation of the connective tissue itself, with formation of rounded or spindle-shaped fibroblastic cells. There is no tendency to

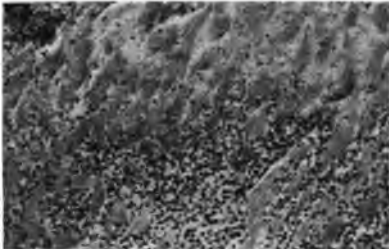


Fig. 200.—Acute myocarditis, showing degeneration of the muscle-fibers and massive accumulation of leukocytes.

suppuration. The blood-vessels are usually somewhat distended with blood, and there may be distinct proliferative thickening of their walls. Degenerative changes of the muscle-fibers themselves are rarely, if ever, absent, and it is most probable that the first stage in the process is a toxic degeneration of the muscle-fibers, and that the intermuscular infiltration and proliferation are consequent upon the primary degeneration. The

fibers become granular and opaque, the striations are indistinct; occasionally there may be vacuolization, and sometimes the segmentation to which so much attention has been directed. Proliferation or swelling of the nuclei of the muscle-fibers is frequent, and the hyaline transformation of Zenker is sometimes observed.

Results.—Under entirely favorable conditions acute, diffuse, and non-suppurative myocarditis usually terminates in complete resolution. It is, however, quite likely that the proliferative changes noted

in the intermuscular connective tissue often advance to complete organization and formation of localized areas of sclerosis. Death from dilatation of the cavities and cardiac failure is not uncommon.

Chronic myocarditis, or fibrous myocarditis, like the acute form, may be diffuse or localized, though in this case the circumscribed form is the more common.

Etiology.—It is not unlikely that many cases are consequent upon acute diffuse myocarditis, as has been already suggested. In such cases the myocarditis may be looked upon as a primary affection. It may be a result of infection with *Spirochæta pallida* or various intoxications. More commonly the process is secondary, and is dependent upon primary disease in, or disturbances in, the circulation of the coronary arteries. It is, therefore, very common to find areas of sclerosis in cases of atheroma of the coronary arteries or in valvular disease of the heart in which the coronary circulation has finally become deficient. In view of the foregoing and the fact that the condition is not accompanied by a continued inflammatory exudate, this condition takes a place with the reparative fibroses. The primary lesion is always degenerative. Among the remote antecedent causes are the conditions which are prone to occasion arteriosclerosis, such as old age, alcohol, gout, syphilis, and the like. The connection between the arterial disease and the resulting myocardial sclerosis has been the subject of considerable dispute. No doubt, in some instances, the circumscribed areas of fibrous overgrowth met with in the distribution of branches of the coronary artery represent the scars of healed infarctions. In other cases, however, it would seem more likely that a slow degenerative change with gradual overgrowth of the connective tissue occurs in consequence of the disturbed circulation through the damaged coronary vessels. Diffuse sclerosis may be associated with hypertrophy in cases of valvular disease and other conditions causing cardiac enlargement. Dehio has suggested that fibroid degeneration or myofibrosis is a conservative process designed to strengthen a heart wall that has become impaired by some degeneration or functional weakness, just as, according to Thoma, the fibrous nodules in arteriosclerosis serve to strengthen parts of the arterial wall that have become weakened by disease of the muscularis.

Localized myocarditis with fibroid overgrowth is very commonly met with at the tips of the papillary muscles in association with chronic endocarditis and disease of the chordæ tendineæ.

Superficial myocarditis of a fibroid character may be seen beneath the pericardium or endocardium which has been thickened by chronic inflammation.

The association of fibroid myocarditis with uterine myofibromata is of some practical importance.

Pathological Anatomy.—The characteristic change is the formation of sclerotic areas in the muscle substance. These appear either as more or less irregular spots, or as streaks or lines running in the direction of the fibers of the heart. They are most common in the anterior wall of the left ventricle, near the apex, in the septum, and at the tips

of the papillary muscles; but the entire substance of the heart may be involved and thickening of the walls may result. The impediment offered to the muscle of the heart by the intermuscular sclerosis may lead to true hypertrophy. Later, there is degeneration of the fibers in

consequence of the pressure of the new-formed tissue, and yellowish areas of fatty degeneration are frequently observed.

Microscopically, the diseased areas are found to consist of more or less well-organized connective tissue lying between the muscle-fibers and pressing them far apart, or taking the place of atrophic muscle-fibers (Figs. 201 and 202).

Sometimes certain portions show the earlier stages of the process, round-cell infiltration and proliferation of the connective

Fig. 201.—Edge of an area of fibrous myocarditis, showing replacement of the fibers by connective tissue (Orth).

tive tissue being the important features (Fig. 203). As a rule, however, the diseased areas are found in a completely organized condition. The muscle-fibers themselves suffer granular and fatty degeneration, and not infrequently distinct vacuolization is observed.

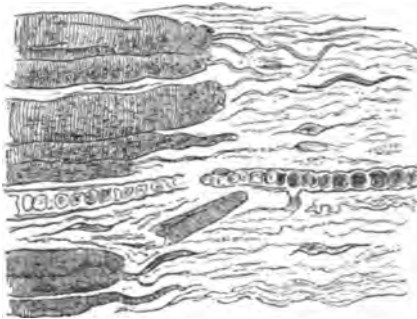


Fig. 202.—Chronic myocarditis, showing extensive destruction of fibers.

Results.—In cases in which a considerable area of chronic myocarditis has developed, as is not uncommonly observed at the apex in consequence of thrombotic or embolic obstruction of the anterior coronary artery, an aneurysm of the heart may result from gradual stretching of the fibroid area. In cases in which the process is diffuse the heart muscle

may at first undergo hypertrophy in consequence of the excessive labor imposed upon it, but eventually degeneration from pressure upon the fibers gains the ascendancy, dilatation of the cavities ensues, and general failure of the circulation is the terminal result.

It is not unusual to find diffuse arteriosclerosis and fibroid disease of other organs associated with chronic myocarditis. In such cases the antecedent cause is the arterial disease, which, in turn, may be dependent upon some systemic disorder.

Pathological Physiology.—The immediate effect of chronic myocarditis or fibroid degeneration of the heart is a loss of power. By some it has been held that the fibroid tissue is designed as a sup-

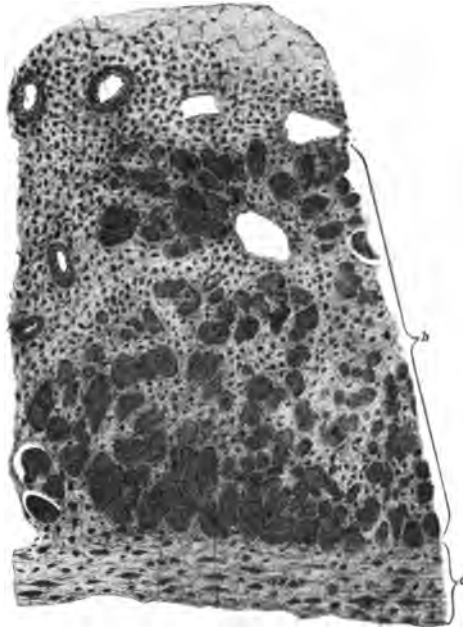


Fig. 203.—Endomyocarditis, showing, *a*, thickened endocardium; *b*, bands of muscle-fibers with interstitial infiltration of round cells and proliferated connective tissue (Bramwell).

port for the heart muscle weakened by other causes, such as degeneration of the muscle-fibers themselves, just as it has been claimed that nodules of arteriosclerosis are intended as support for areas of weakness of the muscular layers of the arterial walls. This theory is not generally accepted; but, on the other hand, it is certain that the presence of fibrous tissue weakens the heart so far as its proper function (contractility) is concerned. For a time hypertrophy of the muscular elements may counterbalance the functional weakness occasioned by the fibroid change, but eventually the muscle fails, and this failure is usually hastened by fatty degeneration and atrophy of the muscle-fibers, which changes, in turn, are doubtless occasioned by the fibrosis,

especially that involving the walls of the small nutrient arteries. In the early stages, with adequate hypertrophy, symptoms may be wanting, though a strong action of the heart and an increase in its size may be detected. Later, progressively increasing weakness of the circulation, and eventually all the signs of cardiac failure develop, just as in advanced valvular disease. Irregularity of the heart's action is much more pronounced than in valvular disease, and is particularly prominent when the walls of the auricles are especially involved. It has been ascribed to implication of the intracardiac mechanism, but no satisfactory demonstrations of this have been made. For the present it can only be said that the irregularity of action results from the disease of the muscle and the consequent disturbance of its automatic contractility and other functions.

Angina Pectoris.—In many cases of fibroid heart, paroxysms of pain occur. These may be moderate in severity and without definite characters, or they may be severe and of a uniform kind. The latter constitute the condition called *angina pectoris*. This is especially marked and frequent in cases of fibroid heart associated with advanced sclerosis of the coronary arteries. The cause of the paroxysms is uncertain. The seizures may possibly be due to minute embolisms and thromboses of branches of the coronary arteries, or to muscle cramp caused by cardiac strain under effort or excitement in cases in which the coronary disease prevents a sufficient supply of blood. The former explanation derives some support from the recognized painful seizures that attend arterial occlusion everywhere, and from the disseminated patches of sclerosis of the heart muscle in cases of fibroid heart with coronary disease and a history of *angina*. These patches of sclerosis may have had their origin in such embolisms or thromboses as are postulated. The muscle-cramp theory has its best support in the analogy of *anginal* paroxysms, with the symptoms of intermittent claudication of the legs in cases of generalized arteriosclerosis. Neither of these explanations, however, suffices for all cases. Changes in the intracardiac ganglia and in the fibers of different parts of the cardiac nervous mechanism have been described, but are of uncertain significance.

HYPOPLASIA AND ATROPHY

Hypoplasia of the heart is a congenital condition in which the heart is insufficiently developed and remains undersized throughout life. This condition is frequently associated with hypoplasia of the aorta and other large vessels, and sometimes with a similar condition of the generative organs. Persons presenting *status lymphaticus* and women who develop *chlorosis* not rarely present the conditions referred to. These individuals are often of delicate structure, with feeble or unstable circulation, and, in the case of males, of effeminate nature and appearance. The heart is small in size and, as a rule, uniformly affected in all parts. The epicardium may be somewhat wrinkled, and this condition, no doubt, has often led to the description

of cases of this sort as instances of atrophy. Many cases of supposed hypoplasia are doubtless instances of true atrophy, the size of the heart being strictly proportioned to the emaciated body.

Atrophy of the heart is usually described as occurring in two varieties, *simple* and *brown atrophy*. It is very doubtful, however, if simple atrophy ever occurs. Many of the cases so designated were doubtless hypoplasias, and other cases probably brown atrophies.

Etiology.—Atrophy of the heart usually occurs in persons of advanced age; but is occasionally met with in the young. It results from simple senility or from various cachectic or wasting diseases, such as tuberculosis, carcinoma, and the like.

Pathological Anatomy.—The heart is small in size, sometimes weighing but a third or fourth of its normal weight. The capsule, or epicardium, is wrinkled, and may be somewhat thickened by fibrous tissue overgrowth or by fatty or mucoid change. The vessels are conspicuously tortuous (Fig. 204). The muscle is flabby and often quite dark in color.



Fig. 204.—Atrophy of the heart, seen from the front (two-thirds natural size) (Bramwell).



Fig. 205.—Brown atrophy of the heart muscle.

Microscopically, the fibers are found smaller than normal and contain excess of pigment. The latter is brownish or black, and at first situated at the poles of the muscle nuclei (Fig. 205). Later the whole fiber may be uniformly pigmented. Sometimes the muscle-fiber is converted into a hollow sheath, containing scattered pigment granules and more or less fragmented nuclei. Complete destruction of the fiber may lead to the apparent occurrence of pigment between the muscle-fibers. The pigment does not contain iron, and seems to be a derivative of the albuminous constituents of the fibers.

Localized atrophy of the fibers may occur around areas of disease of the heart muscle, such as foci of myocarditis, tubercles, gummata, etc. The fibers present the same appearances as those just described.

Pathological Physiology.—Atrophy of the heart muscle does not often occasion striking results or symptoms, as the process is in most

cases commensurate with the general emaciation and decreased demand. Occasionally irregular action of the heart is noted, and sudden death has sometimes occurred.

HYPERTROPHY AND DILATATION

Hypertrophy and dilatation are usually associated and result from the same causes, the degree of hypertrophy or of dilatation present in a given case depending upon the suddenness of action or the intensity of the cause, and upon the state of the heart itself. A sudden strain may cause immediate dilatation; repeated strains of less severity cause hypertrophy in a well-nourished heart, or increasing dilatation in one the seat of myocardial weakness or degeneration.

Etiology.—The influence of valvular diseases (*q. v.*) of the heart in developing hypertrophy has been sufficiently discussed. Various other causes may lead to overwork or cardiac strain, and occasion hypertrophy or dilatation. We may classify the causes in accordance with their operation upon either or upon both ventricles.

Causes Acting on the Left Ventricle.—All forms of arterial disease, but especially diffuse arteriosclerosis, increase the work of the left ventricle notably, and may cause marked changes in it. Aneurysms of the aorta, however, have surprisingly little effect. Chronic Bright's disease, especially the interstitial form, is a well-known cause. It probably acts in several ways: partly by the associated arterial disease, partly by vascular contraction due to toxic products, and partly by the direct stimulation of cardiac action by the same substances. Excessive exercise or laborious occupations (mining, blacksmithing, etc.) may act upon the whole heart, but especially upon the left ventricle.

Causes Acting on the Right Ventricle.—Diseases of the lungs and pleura, such as emphysema, fibroid phthisis, and pleural synechiæ, are frequent causes of hypertrophy and dilatation of the right ventricle.

Causes Acting on the Heart as a Whole.—General functional overstimulation may cause uniform enlargement of the organ. This may be seen in cases of hysteria, exophthalmic goiter, and other diseases in which the overaction is due to nervous influences. Excessive eating and drinking affect the left more than the right ventricle, but influence both sides to some extent. Habitual excessive beer-drinking is most striking in its effects, and doubtless acts through the constantly recurring overdistention of the blood-vessels, as well as through the excess of nutriment and direct stimulus conveyed to the organ. Pericardial adhesions may occasion continuous overaction of both ventricles.

Any of the causes named may occasion hypertrophy or dilatation, or both. The degree of hypertrophy is dependent upon the previous integrity of the heart muscle, the state of the general health, and the manner of action of the cause. Sudden strains are more likely to cause dilatation, and pure dilatation may result if the muscle of the heart is degenerated. This is illustrated by cases of *acute dilatation* of the heart in the course of infectious fevers.

Pathological Anatomy.—Four forms of enlargement of the heart may be distinguished: First, the walls are thickened and the cavities are smaller than normal; this is known as *concentric hypertrophy*, but it is likely that the decreased size of the cavities is due to postmortem contraction; second, hypertrophy of the walls with normal cavities is spoken of as *simple hypertrophy*; third, hypertrophy with cavities of increased size is known as *eccentric hypertrophy*, or *hypertrophy with dilatation*; and, fourth, there may be *pure dilatation* without hypertrophy. In hypertrophy the muscle substance is darker than normal and is increased in consistency. Microscopically, the fibers are increased in thickness, and there is probably also increase in the number of the fibers. The nuclei of the muscle are swollen and multiply; myocardial degeneration (fibrofatty) is often associated. When dilatation is present the heart muscle is usually softer, more flabby, and generally somewhat lighter in color, due to associated degeneration.



Fig. 206.—Hypertrophy of the left ventricle.

The shape of the heart varies from the normal. When the left ventricle is hypertrophied the organ is increased in length and extends further to the left than normal (Fig. 206). When the right ventricle is hypertrophied the organ assumes a rounded shape; its apex is less sharp and the transverse measurement of the organ is greatly increased. The weight and size of the heart may increase enormously, and the term *cor bovinum* is often highly appropriate. Weights of from 500 to 800 gm. are not infrequent, and may be greatly exceeded. Stokes recorded a case in which the weight was 1980 gm.

Pathological Physiology and Results.—Hypertrophy is a relative process which serves to counterbalance the valvular or other impediments to the circulation. Occasionally there may be excessive hypertrophy, but, as a rule, it is merely sufficient to maintain the circulation

under ordinary conditions with less reserve power than is met with in health. In consequence, valvular lesions or arteriosclerosis may occasion no symptoms for a long time, provided the individual leads a quiet life. Eventually, however, when intercurrent diseases have determined cardiac weakness, or when the impediment to the circulation has advanced to an excessive degree, dilatation ensues and failure of the circulation is the consequence. When the left ventricle is at fault congestion of the pulmonary system occurs, and edema, hemorrhage from the lungs, or thrombosis with infarction of the lungs may take place. When the right ventricle fails, general systemic congestion, cyanosis, and dropsy are the consequence.

Great hypertrophy, while it results from arterial disease, very frequently reacts upon the arteries and increases existing arterial disease, or occasions arterial disease when it has not previously existed. This is due to the increased force with which the blood is projected from the ventricular cavity and the increased distention which the arteries suffer in consequence.

ANEURYSM

This is a rare condition of the heart. It is usually found in the anterior wall of the left ventricle, near the apex, but may affect any part of



Fig. 207.—Aneurysm of the left ventricle: the sac through which the probe was passed was situated posteriorly; the unopened aneurysm on the right was anterior; the heart is somewhat twisted out of its usual shape to show both sacs in the illustration (Sailer).

the auricles or ventricles (Fig. 207). Sometimes it is difficult to distinguish simple dilatation from aneurysm. The usual cause of aneurysm is coro-

nary obstruction, with resulting degeneration of localized areas of the wall of the heart. First, there is softening (myomalacia), and this may occasion acute aneurysmal dilatation and even rupture of the heart. In other cases the degenerated area becomes fibrous and subsequently dilates. Acute aneurysm of the heart wall may similarly occur in cases of mural endocarditis. Rupture in such chronic cases is a rare termination.

WOUNDS AND RUPTURE OF THE HEART

Non-penetrating and even penetrating wounds of the heart wall are sometimes recovered from, the injury being repaired by scar-tissue or fibrous myocarditis. As a rule, penetrating injuries occasion rapid death by hemorrhage into the pericardium. Spontaneous rupture of the heart may be occasionally the result of severe strain of a normal heart, but, as a rule, it occurs when there is myocardial disease. Myomalacia cordis, fatty degeneration, malignant endocarditis, and abscess are the conditions most likely to occasion rupture.

INFECTIOUS DISEASES

Tuberculosis may occur in the form of acute miliary tuberculosis, affecting either the endocardium, myocardium, or pericardium; while caseous tubercles result from extension of tuberculous adenitis from the anterior or middle mediastinum.

Syphilis is rare, but may occur in the form of gumma or of diffuse infiltration. In the latter case generalized fibrous myocarditis, indistinguishable in its gross appearances from non-syphilitic cases, may occur. Gummata may lie immediately beneath the pericardium or endocardium, and after softening by degeneration may rupture on the surface. The degenerated areas may be unaccompanied by circumferential reaction, and may go into almost complete resolution without scar-tissue. On the other hand, the fatty area may have about it infiltrative and proliferative inflammation and other degenerations. The spirochetes are numerous in early stages. These areas are replaced by fibrous tissue whether or not they were originally associated with inflammatory processes. They are probably due to colonization of spirochetes.

Actinomycosis may involve the heart by extension from the mediastinum or by embolism. White or grayish nodules are formed, and subsequently degenerate.

NEW GROWTHS AND PARASITES

Primary tumors of the heart are extremely rare. *Sarcoma*, *fibroma*, *lipoma*, *myxoma*, and *myoma* with muscle cells comparable to the cardiac cells have been met with, and usually occur in the form of wart-like growths projecting into the cavities beneath the endocardium. Organized pediculated thrombi have frequently been mistaken for tumors.

Secondary tumors are more common. Sarcomata of the mediastinum may involve the pericardium, or even the heart wall, by direct

extension, while secondary carcinomata and sarcomata may affect the myocardium by metastasis. In the latter instances nodular formations are seen embedded in the heart muscle.

Parasites.—Echinococcus cysts are occasionally seen beneath the endocardium or pericardium, and may rupture into the cavities of the heart, with resulting embolism. The cysticerci of *Tenia solium* and of *T. saginata* have occurred in man, but are more common in animals. The larval *Linguatula rhinaria* is a rare parasite of the heart.

THE PERICARDIUM

The pericardium is a membranous sac enclosing the heart and the root of the great blood-vessels. It is composed of a fibrous outer layer, and is lined within by flat endothelial cells. Normally it contains from 5 to 50 c.c. of clear serous liquid.

Partial or complete absence of the pericardium is sometimes seen, especially in cases of ectopia of the heart. Occasionally diverticula are present congenitally.

CIRCULATORY DISTURBANCES

Hyperemia of the pericardium may occur in valvular heart disease or in cases of tumor or aneurysm causing intrathoracic pressure.

Hemorrhages.—Extreme passive congestion with ecchymotic hemorrhages is found postmortem in cases of death from asphyxia. Small punctate hemorrhages are also occasioned by various infectious diseases and by certain poisons, as phosphorus. They are also seen in pernicious anemia, scurvy, purpura, and other blood diseases.

Hemopericardium is a term applied to accumulation of blood in the pericardial sac. It may result from rupture of the heart or of aneurysms of the aorta, pulmonary artery, or coronary arteries. The serous effusion of inflammatory conditions of the pericardium may sometimes contain considerable blood which has escaped from the small blood-vessels in the inflamed tissue. This is more common in inflammatory effusions of the pericardium than of other serous membranes, and is particularly true of tuberculous and cancerous cases.

Hydropericardium, or dropsy of the pericardium, may occur when passive congestion is continued, or as a part of anasarca. Occasionally the liquid is milky (*chylous hydropericardium*).

INFLAMMATION

Inflammation of the pericardium, or **pericarditis**, is the most important pathological process affecting this serous sac.

Etiology.—Pericardial inflammations may be *primary* or *secondary*. In the former the irritants are conveyed to the pericardium through the blood, while in the latter the inflammation results from extension. Primary pericarditis occurs in association with various infectious diseases, notably acute rheumatism, scarlet fever, small-pox, influenza, and

intense septic infections. These cases are termed "primary" because they are not extension processes, but hematogenic. It is also met with in the course of nephritis, either acute or chronic. Secondary pericarditis may result from extension of inflammation from the pleura, the lung, the mediastinal glands, the sternum, the esophagus and stomach, or from the heart itself.

In many instances, even when the pericarditis has occurred in the course of an infectious disease, micro-organisms are not discovered in



Fig. 208.—Acute pericarditis (Bramwell).

the exudate; this may be due to the arrest of the micro-organisms in the pericardial tissues; staphylococci, streptococci, pneumococci, and tubercle bacilli have all been found.

Pathological Anatomy.—Several varieties may be distinguished, though one form may merge into another.

Fibrinous or Dry Pericarditis.—The first change noted in pericarditis is a dulness or lusterless condition of the surface of the membrane. Somewhat later distinct granulations, or a thin coating of fibrin, appear upon the surface, and this may increase until the deposit has a notable

thickness. The movements of the heart may give the latter a marked roughness or rugosity, and the term applied by older writers, *cor villosum*, is not inappropriate (Fig. 208). Microscopically, there is seen a deposit of granular or fibrillar fibrin upon the surface, while the endothelial cells are loosened and partly degenerated, and the subendothelial tissues are infiltrated with round cells. The blood-vessels are generally widely dilated, and punctiform hemorrhages may be observed.

Serofibrinous Pericarditis.—The pericardial exudate rarely remains purely fibrinous in character. Usually there is some serous outpouring, and the sac becomes distended with more or less abundant turbid, serous liquid, in which flakes of fibrin are suspended. In such cases the fibrinous deposit is generally slight. Later the fluid may be reabsorbed, leaving a simple fibrinous pericarditis.

Purulent pericarditis, or pyopericardium, may begin as a fibrinous or serofibrinous process, or it may assume the suppurative form from the very start. In these latter cases the cause of the pericarditis is usually some intense general infection, as in puerperal pyemia and septicemia, or it may be a local infection, as in cases in which an esophageal or gastric ulceration has ruptured into the pericardium, or in which a caseous tuberculous focus or purulent pleurisy has found a similar discharge. The pericardial sac is filled with purulent or seropurulent liquid, and the pericardium itself is covered with fibrinopurulent exudate. The superficial layers of the myocardium are frequently involved by inflammatory edema, myocarditis, or fatty degeneration.

Hemorrhagic pericarditis is met with in individuals of low vitality and in persons suffering from scurvy, purpura, and similar affections. Pericarditis accompanying tuberculosis or cancer of the pericardium is specially prone to assume a hemorrhagic type. Usually the exudate is serous, but distinctly colored with blood; sometimes it is almost completely hemorrhagic.

Terminations of Acute Pericarditis.—Any of the forms described may persist for a considerable length of time without change, but usually certain alterations are noted. In the fibrinous variety or in the serofibrinous form, after the liquid has been reabsorbed, the visceral and the parietal pericardium lie in contact and are agglutinated by the exudate. Gradually the inflammatory processes beneath the fibrinous exudate extend into the fibrinous coating; connective-tissue hyperplasia and new formation of blood-vessels follow, and granulation tissue unites the adjacent layers of pericardium. At the same time the fibrinous exudate is reabsorbed and subsequently organization of the granulation tissues is completed. Fibrous adhesions binding the two layers of the pericardium together ensue, and at times complete obliteration of the sac is the consequence (Figs. 209 and 210). In cases in which the inflammation is slight, or in which the layers are kept apart by persistent serous exudate, the areas of inflammation gradually become thickened by new-formed fibrous tissue, and there remain upon the surface of the pericardium sclerotic spots, often spoken of as "milk spots." Occasionally portions of the fibrinous exudate remain unabsorbed, and

together with the thickened membrane itself and the adhesions suffer calcareous infiltration. The heart may thus be encased in calcareous plates of considerable thickness. An infrequent termination is the



Fig. 209.—Adhesive pericarditis, showing fibrin deposit, with new blood-vessels extending upward into it (Perle).

retention of tabs of thick fibrin, covered by connective tissue, containing considerable fluid. These give the impression of small pedunculated cysts.

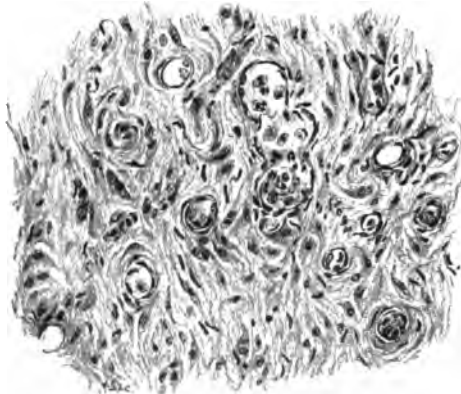


Fig. 210.—New blood-vessels and fibroblastic cells in a beginning adhesion of the pericardial layers.

Purulent pericarditis may terminate by discharge of the exudate into the esophagus, stomach, pleura, or even into the bronchi, and by

the subsequent adhesion of the two layers of the sac. In other cases gradual inspissation of the pus takes place and the cheesy residue may remain or eventually become calcareous.

Associated Conditions.—While, on the one hand, pericarditis often follows inflammatory processes in the surrounding parts, it, on the other hand, not infrequently occasions disease of the adjacent structures. In most cases of severe acute pericarditis there is some associated inflammation of the mediastinal structures and of the pleura contiguous to the pericardium. Cases which terminate with the formation of fibrous adhesions within the pericardial sac usually also present mediastinal and pleural adhesions with the external surface of the pericardium (*pericarditis interna et externa*). Myocarditis extending to a depth of 1 or 2 mm. is seen in nearly every case of pericarditis. In cases in which considerable pericardial exudate is present the heart muscle is pressed upon and impeded in function, so that venous congestions are commonly observed. Adhesive pericarditis leads to hypertrophy and, later, dilatation of the chambers of the heart.

INFECTIOUS DISEASES

Tuberculosis of the pericardium may result from the extension of pulmonary or pleural tuberculosis, or of tuberculous affections of the mediastinal glands. More rarely direct infection may occur through the medium of the circulation. Miliary tubercles are formed in the subserous and serous layers of the membrane, while the surface is covered with fibrinous exudation. The attendant pericarditis may be entirely fibrinous and the tubercles may be hidden from view by a thick deposit. In other cases there is serous, hemorrhagic, or purulent exudation, the latter especially in cases in which vomicae containing infective matter have ulcerated into the pericardial sac. Tuberculous pericarditis may terminate by gradual absorption of the exudate and fibrous adhesion, sometimes with calcareous infiltration. In other cases the necrotic and destructive changes characteristic of tuberculous processes elsewhere gain the ascendancy, and the disease proves fatal by the seriousness of the cardiac involvement.

Syphilis is an extremely rare condition. Certain indurative changes in the pericardium have, however, been met with in association with syphilis of the heart.

Actinomycosis may result from extension of actinomycosis of the mediastinum or of the lungs.

TUMORS AND PARASITES

Primary tumors, such as lipoma and fibroma, are extremely rare. Secondary carcinoma and sarcoma are more frequent. They result from similar growths in neighboring structures. Hydatid cysts and cysticerci are occasionally met with.

PNEUMOPERICARDIUM

Pneumopericardium (air in the pericardium) may result from perforation of the sac in cases of fracture of the ribs or from penetration of foreign bodies through the esophagus into the pericardium. It also results from rupture of gastric or esophageal ulcers, and a certain amount of gaseous accumulation complicates purulent pericarditis when the exudate undergoes decomposition. The association of air and pus (*pneumopyopericardium*) more often results from secondary purulent inflammation after the development of pneumopericardium.

THE ARTERIES

Anatomical Considerations.—The arteries and veins consist of three coats, called, respectively, the *intima*, or inner coat; the *media*, or middle coat; and the *adventitia*, or external coat. The intima consists of a layer of endothelial lining cells, below which there is a thick fibrous layer and then an elastic membrane. The middle coat consists of smooth muscle- and elastic fibers, while the outer coat is composed of fibro-elastic tissue. Small blood-vessels, the *vasa vasorum*, ramify through the adventitia and outer media, but the intima and immediately subjacent media are avascular, and probably nourished from within the vessel.

CONGENITAL DEFECTS

Certain defects of distribution and of origin of the larger trunks have been referred to in the discussion of congenital defects of the heart. Very commonly there are anomalies in the arrangement of the peripheral branches, but these are merely of anatomical interest.

Hypoplasia.—A condition of importance is congenital smallness, or hypoplasia. This may affect the aorta and larger vessels together with the heart, or it may be confined to the blood-vessels, the heart being normal. Vascular hypoplasia has been especially met with in chlorotic girls, and also occurs in cases of status lymphaticus. The aorta is sometimes so small that it barely admits the little finger, and the walls are usually correspondingly decreased in thickness. Decided elasticity of the coats of the vessels may be observed.

HYPERTROPHY

This occurs when a collateral circulation is established in consequence of obstruction of an artery. Similarly, in the new formation of tissue the blood-vessels first formed are delicate vascular channels, which subsequently hypertrophy and are converted into well-developed arterioles. In this case there is a uniform overgrowth of each of the component parts of the blood-vessel, and not a mere hyperplasia of one or another coat.

ATROPHY

This may occur in a part which is undergoing general atrophy, or where there is pressure and anemia of certain areas. Degeneration of the walls usually takes place in such cases, and the conditions are, therefore, more properly considered among degenerations.

DEGENERATIONS

Fatty Degeneration.—Any one of the coats may be affected, but the process is most common in the intima. Fatty degeneration is one of the important factors in atheroma; more rarely it occurs as an independent affection of the blood-vessels. In the latter case disturbances of circulation and toxic agencies in the blood are the immediate causes. Small white or yellowish spots or streaks may be seen in the endothelium, and microscopically the endothelial cells may be found granular or filled with fat-drops. In cases of greater severity there may be actual erosion of the endothelial surface. In cases in which the media is affected the muscle-cells undergo fatty degeneration. Fatty degeneration may occasion rupture of the blood-vessels, or calcareous infiltration may ensue.

Calcareous infiltration is the common termination of atheroma, but sometimes calcification of the intima or media, or even of the entire wall of the vessel, may be observed without arteriosclerosis. The process is most common in the intima and media, and, aside from the instances in which it is a part of atheroma, it may occur in consequence of circulatory disturbances, or as the result of bone disease, with destruction of osseous tissue and surcharge of the blood with earthy salts.

Hyaline degeneration is a condition the nature and uniform character of which remain in doubt. A form of hyaline degeneration is very common in the hyperplastic tissue of arteriosclerosis, and is generally the first evidence of beginning degeneration. It is met with in small blood-vessels which are obstructed by thrombi, or which are subjected to destructive pressure by inflammatory new growths or other causes. Not infrequently it is due to infectious fevers or intoxications, and in these cases the small arteries and the capillaries are prone to be affected. Hyaline degeneration of the blood-vessels is the striking feature of certain cylindromata (see Fig. 70). The artery may show a uniform or a more nodular, firm, opaque thickening, and under the microscope the subendothelial tissue, the adventitia, or the entire wall of the blood-vessel may be found converted into vitreous substance. Rupture of the affected vessel is a not infrequent result.

Amyloid infiltration commonly begins in the blood-vessels of the parts of the body in which this disease is found. In the kidneys the capillary tufts of the Malpighian bodies, and in the spleen the capillaries within the follicles, are first affected. In these cases the entire wall of the vessel is involved, and presents the characteristic appear-

ances of the disease. Amyloid disease is sometimes found in the intima of the larger blood-vessels, occurring in small linear or punctate areas, and scarcely to be recognized excepting by chemical tests.

INFLAMMATION

Inflammation of the arteries may affect the inner, the middle, or the outer coat, and in a strict anatomical sense the terms *endarteritis*, *mesarteritis*, and *peri-arteritis* are justified; but, as a rule, all three coats are more or less involved at the same time, and no practical distinction can be drawn. There may be acute or chronic inflammation.

Acute Arteritis

Acute arteritis may be of two kinds: a suppurative or necrotic form and a productive form.

Acute suppurative arteritis occurs in the arteries traversing areas of suppurative inflammation, and results from the extension of the suppurative process. It may also occur in consequence of the lodgment of infected emboli or as a result of infection of thrombi within the vessels.

When the process extends from without, the adventitia and then the media are infiltrated with round cells, and in cases of some of the larger vessels there may be visible points or collections of pus. The process may extend as deeply as the intima, and may completely perforate the wall of the vessel, leading to hemorrhage. The intima itself is not directly involved by the suppurative process from the lack of independent blood-supply, but the emigrated leukocytes may infiltrate it, and degenerative changes are common in the endothelium. Where the process begins by infection within, as through softened thrombi or infectious emboli, there is first necrotic or degenerative destruction of the intima, and subsequently infiltration of the media and adventitia with emigrated round cells (Fig. 211).

A form of infectious arteritis resembling malignant endocarditis has been observed in association with that condition in a few instances. Ulcerated patches are seen in the intima of the aorta, and acute aneurysmal dilatation or even perforation has been met with.

Acute productive arteritis (also called **proliferating** or **obliterating**, according to its result) is most commonly the result of tissue changes surrounding the arteries, and is, therefore, constantly met with in diseases of organs leading to overgrowth of connective tissue. The condition is chronic rather than acute in such instances. Acute productive arteritis also occurs as a consequence of thrombosis, either of non-septic embolic origin or arising *in loco*, within the blood-vessels when the latter are not infected. The term *thrombo-arteritis* has been applied to these cases. It is by thrombo-arteritis that wounds of vessels are closed and the lumen of the blood-vessels at the point of ligation permanently obliterated.

It has been asserted that generalized *thrombo-angiitis* is an infective process or has infiltrative, if not, indeed, suppurative, lesions as its characteristic early manifestation. It is most often seen in the extremities associated with subcutaneous nodosities.

The changes affect mainly the intima and the adventitia, both of which coats are densely infiltrated with round cells. The thrombus, which was the original cause of the arteritis or which has resulted therefrom, becomes similarly infiltrated with round cells, and as the process advances is found to be penetrated by fibroblastic cells, which probably take origin from proliferation of the endothelial lining cells or from other connective-tissue cells in the walls of the vessels. New blood-

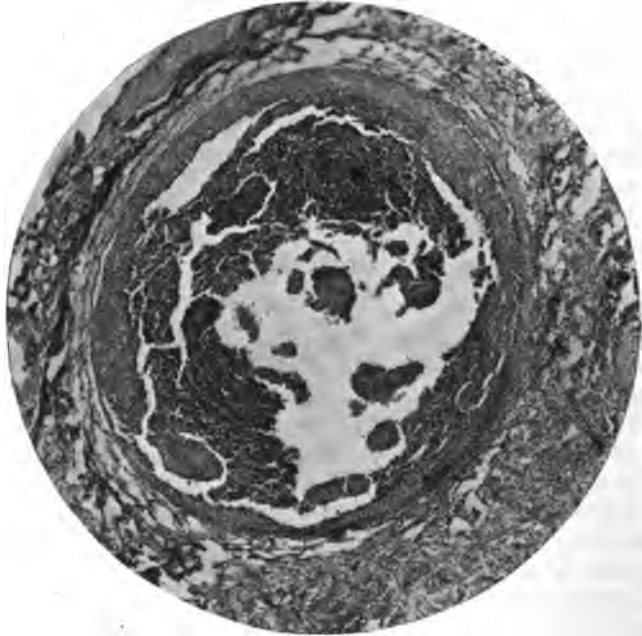


Fig. 211.—Septic thrombo-endo-arteritis of coronary in vegetative endocarditis.

vessels spring from the *vasa vasorum* and penetrate the thrombus, and a lesser number of new vessels may enter the thrombus directly from the lumen of the occluded vessel itself (see Fig. 8). The process of organization takes place as in the serous surfaces generally, and as new connective tissue is formed the thrombus is gradually removed and the lumen of the vessel may become completely obliterated (*endarteritis obliterans*). Less extensive involvement of the vessel may lead to the formation of bands of adhesion passing from one side of the vessel to the other, and causing considerable deformity and distortion. In other cases there may be merely thickening of the intima as a final result, the thrombus having been washed away or absorbed. The media usually takes very little part in the process, being merely infiltrated with round cells, but the

entire wall of the vessel may become fibroid in the terminal stages and the separate coats may be indistinguishable.

Peri-arteritis Nodosa.—Under this name has been described a form of productive inflammation of the adventitia leading to the formation of fibrous nodules. In some of these cases there is no doubt a different pathology, as in the instances in which the intima has been found to protrude in a hernia-like manner through defects in the media, but in most cases the disease is a productive peri-arteritis (see also under Aneurysm). The medial changes seem secondary, this coat showing necroses and hemorrhages, and finally atrophy. Intimal thickening occurs later. The disease is an acute one frequently and has been ascribed to syphilis. The etiology cannot always be established.

Arteriosclerosis

Arteriosclerosis, or endarteritis chronica deformans, is a chronic degenerative and inflammatory disease of the arterial system. It may be confined to the arteries, or may be more extensive, involving the capillaries as well, when the term *arteriicapillary fibrosis* (Gull and Sutton) is applicable. Sometimes the veins also are involved, and for this condition the name *angiosclerosis* has been proposed.

Etiology.—Arteriosclerosis is a physiological process of old age, and probably begins as early as middle life in most persons. The earlier occurrence of the disease or the more extreme grades of its severity are dependent upon a variety of causes, among which certain chronic intoxications—viz., syphilis, gout, chronic alcoholism, and chronic nephritis—are prominent. An important cause is muscular exertion, and it is not uncommon to find marked instances in persons whose life or occupation has subjected them to unusual muscular strain. Cachectic conditions of various kinds may play a part, as in cases of carcinoma, tuberculosis, or inanition; and sometimes the chronic arterial disease follows after acute infections, such as rheumatism, scarlet fever, typhoid fever, and the like. Overfeeding may be an important cause.

Pathogenesis.—Not a little difference of opinion has existed in regard to the manner in which the recognized causes of arteriosclerosis operate. At first it was generally maintained that the infectious and toxic agencies directly irritate the inner lining of the blood-vessels and produce inflammatory thickening. This view has, however, been quite generally abandoned, and it now seems established that degenerative changes and loss of elasticity in the vessel wall are the result of the primitive causes, and that the hyperplastic processes in the intima and other parts of the arterial wall are the ultimate expression of a reparative process.

In cases of arteriosclerosis occurring in old age, for example, the first disturbance of the blood-vessel consists in a loss of elasticity in the muscularis and an overdilatation of the blood-vessels. Secondly, in consequence of this loss of elasticity, there is a hyperplasia of the intima, which serves in some measure to contract the lumen of the

vessels and thus restore the vascular channels to their normal calibre. In cases of purely pathological arteriosclerosis similar functional weakness of the muscularis or more pronounced and demonstrable degenerative changes may be the primary conditions, which in the end lead to arteriosclerosis. In all cases the direct effect of elevations of blood-pressure may play an important part, and in cases of muscular overwork or of hypertrophy of the heart the increased vascular tension may be the all-important cause. It may be said that generally sclerotic changes occur most frequently in vessels that feel, or are subject to, frequent alterations in blood-pressure.

In explaining the minuter origin of the vessel-wall changes one must think of those which begin as a chronic productive inflammatory process and those in which the change is degenerative at first. The line between is by no means sharp, and the latter may be but a forerunner of the former. The inflammatory kind is exemplified by syphilitic arteritis (*q. v.*); the degenerative, by the senile form.

It has been supposed by some that degenerations of the media, with giving away of its muscular, elastic, and fibrous tissue, are due to compression by proliferated intimal endothelium acting under toxic influences. These alterations have been explained by others as purely toxic degenerative medial changes. Regardless of inception, the proliferation of the intima and the degenerated media are replaced by connective tissue or by atheroma. In the senile form, granular, fatty, and calcareous degeneration of the media is the first change. Aschoff has suggested that in some way plasma penetrates the vessel walls, liberating colloids and inorganic salts which would act as a starting-point of degenerative or proliferative processes.

In the Mönckeberg type of sclerosis, affecting either large or small vessels, the medial coat is most prominently affected. Degeneration and calcification appear early, the muscle-fibers shortly disappear, and with the loss of tissue, which acts to regulate the caliber of the vessel, irregular dilatation of the lumen results.

Pathological Anatomy.—Arteriosclerosis may be a *diffuse* process, affecting more or less uniformly a large part of the arterial system, or it may be a *circumscribed* or *nodular* condition. In the latter instances, which are most common in the aorta and large vessels, there are seen on the inner lining of the vessel nodular elevations, varying from the merest points to areas the size of a small coin. These are raised a millimeter or two above the surface, and in their earlier stages have a translucent grayish color; they are covered with smooth, unaltered endothelium. Later, degenerative changes ensue and the nodule becomes dull-white or yellowish in color, and finally calcification may render it extremely hard (*atheromatous plate*). The focus may, on the other hand, soften completely by degeneration and may discharge into the lumen of the vessel, leaving a necrotic, ulcerated patch (*atheromatous ulcer*). Calcareous change may now occur, and the surface may be covered with thrombotic fibrinous deposits. These circumscribed areas of arteriosclerosis may be few in number and widely separated. In such

cases the openings into the coronary arteries and the other branches of the aorta are the favorite seats. In other cases the plates may be so numerous and thickly set that the aorta is completely transformed.

Diffuse arteriosclerosis is especially frequent in elderly persons, and is more common in the small vessels than in the aorta. Sometimes it is associated with the nodular form; sometimes the nodular change is wanting.

Microscopically, the nodular elevations are found to consist of dense sclerotic tissue in which deeply staining cells of elongated character may be visible, the hyperplasia affecting the subendothelial part of the intima in the earliest stages (Fig. 212). There is swelling of the endothelia, with fatty detritus and globules collecting in these cells, possibly the collection of fibrin upon the surface, and the appearance of polynuclears. Subsequently degeneration of the nodule becomes manifest. At first the intercellular material assumes a hyaline character and becomes glassy in appearance. The cells themselves may suffer fatty



Fig. 212.—Transverse section of a cerebral vessel, in a case of *endarteritis nodosa* (Birch-Hirschfeld).



Fig. 213.—Atheromatous degeneration of a cerebral artery (Karg and Schmorl).

degeneration from pressure. Later the whole area undergoes myxomatous or, more particularly, fatty degeneration, and breaks down, forming a pultaceous detritus in which fat-drops and cholesterol plates are prominent (Fig. 213). Eventually calcareous granules are deposited. In diffuse arteriosclerosis the changes resemble those met with in the nodular form. There is widespread thickening of the arterial coats in-

volving the subendothelial tissue at first and later the entire wall. Secondary degenerative changes in areas or patches occur in the large arteries, but are less common in the small vessels. The endothelium attempts repair over defects except calcareous ulcers. It is heaped up over subintimal and medial swellings.

Fatty degeneration and calcification may also be apparent in the media, and more or less hyperplastic connective-tissue overgrowth may be seen in the adventitia. In cases of diffuse arteriosclerosis the media, as a rule, is thickened by hypertrophy of the muscle-fibers as well as by sclerosis; but in the nodular forms the media is usually distinctly thinner than normal. This hypertrophy only affects those that are wholly intact and is compensatory, as destroyed media muscle-fibers do not regenerate. Repair occurs in direct relation to the freedom of blood-supply to the diseased parts, either from the *vasa vasorum* or from the lumen of the affected vessel. This brings nutrition and stimulates cells of the fibroblastic series. Even elastic fibers may be restored. Köster pointed out that round-cell infiltration surrounding the small branches of the *vasa vasorum* in the media is the earliest change in some instances. Rupture of the elastic coat is doubtless an important early change in many cases. Considerable round-cell infiltration may be seen in the deeper layers of the intima and in the media, and new formation of blood-vessels may be quite pronounced. Such changes, however, are not usual and not characteristic.

Results.—In the smaller blood-vessels, particularly in those of the brain, the hyperplastic process in the intima may proceed to such a degree that the lumen of the vessels is almost completely obliterated (*endarteritis obliterans*). Complete obliteration may take place by direct union of the opposite walls of the vessel, or there may be first thrombosis, with subsequent organization of the thrombus. In the aorta and in some of its larger branches the loss of elasticity consequent upon the formation of fibrous tissue and subsequent degenerations leads to gradual dilatation of the blood-vessel walls, either in the form of diffuse ectasia or of localized aneurysmal sacs. Sometimes the degeneration of the diseased area occasions spontaneous rupture of the vessel.

Portions of the thrombotic deposits upon the roughened lining of the vessels, or portions of the degenerative tissue itself, may be discharged into the circulation, and may be carried to the peripheral parts as emboli.

Changes in Other Organs.—Diffuse arteriosclerosis places an impediment upon the heart which leads to hypertrophy of its walls, and, in particular, of the walls of the left ventricle.

When the process affects the small blood-vessels in the substance of the various organs, degenerative changes due to anemia and reactive hyperplasia of connective tissue are common results. Thus, in cases of sclerosis affecting the cerebral vessels, cerebral softening is commonly met with, while in cases in which the branches of the coronary or of the renal arteries are affected, degeneration and fibroid changes are seen in the heart and kidneys.

INFECTIOUS DISEASES

Syphilis may involve the blood-vessels in a variety of ways. No doubt syphilitic infection is a most potent cause in the production of arteriosclerosis, but more specific involvement of the vessels occurs. Recent investigators have described a special type of arteriosclerosis as syphilitic. In this the ascending aorta is often notably affected, the lesions presenting themselves as scar-like changes which cause marked deformity of the endarterial surface. This can proceed toward the heart and affect the valve bases or the leaflets themselves. Microscopically, the media and adventitia are much more decidedly involved than in ordinary arteriosclerosis. The process begins as a perivasa-vasorum infiltrate of round cells in the media and adventitia, shortly followed by atrophy of muscularis and elastica. In areas of syphilitic infiltration and induration or adjoining gummata the small blood-vessels present noteworthy changes. The intima and the adventitia, but particularly the former, undergo great hyperplasia, and the lumen of the vessel may be almost obliterated. The changes are first noted in the intima, where large numbers of epithelioid cells are formed, while, later, infiltration of round cells is observed. The adventitia is similarly, but less extensively, affected. The outcome of this arteritis is fibrous scar-tissue; atheroma and calcification occur very seldom in pure syphilitic arteritis. The scar-tissue, while dense, is without elasticity, so that at the points of cicatrization variations of lumen occur (syphilitic aneurysms, *q. v.*).

Tuberculosis.—The arteries may become involved in areas of tuberculosis, though, as a rule, they prove resistant for a long time. Typical caseous degeneration may be seen in the walls of the blood-vessels, beginning in the adventitia and gradually advancing toward the interior. In the lungs these changes are not infrequently seen in the walls of tuberculous cavities, and as a result there may be small aneurysmal dilatations at the points where the wall of the vessel has become eroded and weakened. It is from such vessels that the severe hemorrhages of the late stages of phthisis take place. Sometimes the blood-vessels of the tuberculous area present productive change leading to great thickening of the adventitia and of the intima, and there may be considerable narrowing of the lumen of the vessel. This, however, is less common than the degenerative changes before alluded to. There may be solitary tubercles in the intima or subintimal layers of the media. They are of ordinary architecture and may open into the vessel lumen. They start as endothelial tubercles when the organisms are taken up by these lining cells in capillaries.

ANEURYSM

Definition.—By aneurysm is meant a more or less localized dilatation of the arterial walls. The term has, however, been applied also to collections of blood outside of an artery enclosed by an adventitious

wall and consequent upon a rupture of the vessel. The name *false* or *spurious aneurysm* has been specially applied to such cases, while the term *true aneurysm* is reserved for such as conform to the first definition. It is preferable to confine the single word aneurysm to the latter.

Etiology.—Aneurysms are always due to some weakness of the walls of the blood-vessel and to the distending force of the blood within. It is, therefore, most common to find the disease in persons beyond the age of forty or forty-five years, and particularly in those who have acquired arteriosclerosis. Among the remote causes, therefore, are those of arterial disease—syphilis, gout, alcoholism, lead-poisoning, and other chronic intoxications. *Of all the causes, syphilis is most important.* Sometimes it would seem



Fig. 214.—Worm aneurysm of the horse (Leuckart).

that there is hereditary weakness of the arterial coats, and instances of aneurysm occurring in successive generations have been recorded. Even congenital aneurysms have been observed. As contributing causes may be ranked all conditions which increase the blood-pressure. Thus, laborious occupations, hypertrophy of the heart, and diseases which occasion constant excess of blood-pressure give rise to arterial degeneration and also to dilatation of the vessel in a purely mechanical way. Sudden aneurysmal dilatation of a weakened vessel may occur after severe straining efforts, as in coughing, during labor, in the straining of obstinate constipation, etc.

More acute degenerative changes in the blood-vessels may lead to aneurysmal dilatations. Thus, in the rare instances of acute aortitis in association with malignant endocarditis, small aneurysmal dilatations and even rupture of the aorta may occur. Embolism plays a part in a similar manner. Sometimes a calcareous embolus from a diseased valve of the heart, or from an atheromatous plate in the aorta, may lacerate the walls of a peripheral vessel, leading to the formation of a dilatation. In other cases infected emboli (as in malignant endocarditis or thrombosis with secondary degeneration of the clot) lodge in the peripheral vessels and occasion acute inflammatory or degenerative lesions of the walls, and eventually aneurysmal dilatation. These cases are analogous to the aneurysms of lower animals caused by animal parasites (Fig. 214).

The artery most commonly affected is the aorta, and in particular the thoracic portion. A majority of the aneurysms affecting the thoracic

part of this vessel arise from the ascending limb, and not rarely it is one of the sinuses of Valsalva that first suffers dilatation. Next to the aorta in point of frequency, the popliteal, femoral, carotid, subclavian, innominate, axillary, and iliac vessels are affected.

An interesting form, and one of great frequency and clinical significance, is that which affects the small blood-vessels of the brain, particularly the branches supplying the lenticulostriate body. This is the so-called *miliary aneurysm*, which is commonly the cause of cerebral hemorrhage (Fig. 215). It is simply a small saccular aneurysm due to weakening of the blood-vessel walls by sclerosis or degeneration.

In some cases of the condition described as *peri-arteritis nodosa* (see p. 507) there has been discovered a hernia-like projection of the intima through defects of the media. These have been recorded as instances of congenital aneurysm, but this explanation does not suffice for all cases. (See Arteritis.)

In phthisical lungs there are often found somewhat similar hernia-like aneurysms, due to erosion of the adventitia and media by the tuberculous process; and it is from these that the severe hemorrhages of the late stages of phthisis occur.

Pathological Anatomy.—Aneurysms may be of three kinds: (1) Those in which there is quite general dilatation of all of the coats of the vessel, which, therefore, present themselves in the form of a more or less uniform dilatation (*ectatic aneurysm*); (2) those in which a local weakening leads to the formation of a saccular pouch, often communicating with the artery by a narrowed orifice (*saccular aneurysm*); and (3) those in which a rupture of the intima, and usually of portions of the media as well, has led to infiltration of blood between the tunics of the vessel wall (*dissecting aneurysm*).

1. **Ectatic Aneurysm.**—There is more or less uniform dilatation in these cases, and there may be distinguished *fusiform* or *spindle-shaped* and *cylindrical* varieties, according to the shape assumed (Fig. 216). In some instances the vessel is rendered tortuous by the unequal involvement of different portions, and to this form the term *cirroid aneurysm* may be applied. The same term, as well as the name *anastomotic aneurysm*, is given to certain conditions of the arteries of the scalp and other parts which lead to the formation of tortuous vessels standing out prominently beneath the skin; but these are instances rather of hypertrophy of the coats, with increase of length and thickness of the walls, without, in reality, any aneurysmal dilatation at all.

In ectatic aneurysms the intima and adventitia are usually thickened, and there are generally atheromatous patches in the former. The media is generally thinner than normal, and may be actually deficient in places. Ectatic aneurysms may show a certain amount of thrombosis in the form

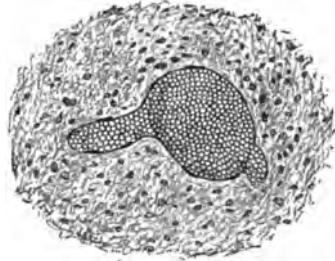


Fig. 215.—Miliary aneurysm of the brain.

of laminated clots, when there are pouchings or inequalities in the dilatation, but very frequently there is no thrombosis.

2. Saccular Aneurysm.—This is the most important variety. According to Thoma and others, the first step in the process is the weakening or giving way of the media, followed by gradual dilatation of the intima and adventitia. There results a saccular dilatation communicating with an artery, from which it arises by a more or less narrow orifice (Figs. 217–219). The aneurysmal sac grows larger and larger, and

may eventually rupture; but even then a secondary retaining wall may be formed by condensation and reactive hyperplasia of the surrounding tissues. The wall of the aneurysmal sac consists of thickened adventitia



Fig. 216.—Cylindrical and somewhat cirroid aneurysm of the abdominal aorta: an opening has been made to show the clot within (from a specimen in the Museum of the Philadelphia Hospital).

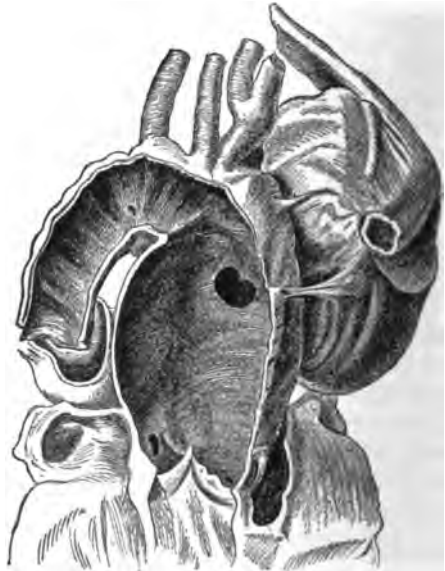


Fig. 217.—Saccular aneurysm of the arch of the aorta, projecting forward and attached to the ribs (Ziegler).

and intima, the media being usually thinned and often completely wanting. The intima is generally covered with atheromatous plates, and the cavity, as a rule, contains more or less abundant laminated clots, which tend to contract and organize, or to suffer subsequent degeneration. The aneurysm, if small, may be completely healed by the organization of the clots within.

The tissues surrounding the aneurysm are pushed aside or compressed, and may suffer extensive necrosis. In cases of aneurysm of the thoracic aorta the sternum and ribs may be eroded, and the aneurysm

may project beneath the skin anteriorly and eventually rupture (Fig. 220). In other cases the trachea, bronchial tubes, or lungs are compressed, and rupture takes place through the trachea or bronchi (Fig. 221). In still others the sac projects posteriorly, erodes the bodies of the vertebræ and ribs, and may compress the spinal cord or may project beneath the tissues of the back. Occasionally, communication is established with the large venous trunks, particularly the descending vena cava. Complete arrest or cure of an aneurysm may take place by organization of the clots contained, but such a result is rare.



Fig. 218.—Saccular and partly ectatic aneurysm of the descending part of the arch of the aorta (from a specimen in the Museum of the Philadelphia Hospital).



Fig. 219.—Saccular aneurysm of the ascending part of the arch of the aorta (from a specimen in the Museum of the Philadelphia Hospital).

3. **Dissecting aneurysm** is most common in the aorta. As the result of degenerative lesions or of mechanical injury rupture of the intima occurs, and the blood finds its way between the coats of the artery, often burrowing to considerable distances. In a case under the observation of one of the authors the walls of the aorta were dissected as far as the bifurcation, where secondary ruptures had occurred in the intima (Fig. 222). Usually the dissection takes place in the media, which is thus separated into two parts. Subsequently the adventitious canal may become lined with endothelium, and in the case quoted atheromatous plates had formed in the latter.

Associated Conditions in Other Parts.—Some hypertrophy of the heart may occur when an aneurysm is situated near the root of the aorta, and particularly in instances in which direct pressure is brought



Fig. 220.—Aneurysm of the aorta: erosion of the sternum and projection of the sac beneath the skin.

to bear upon the heart. As a rule, however, the amount of hypertrophy is much less than might be expected. Pressure upon the venous



Fig. 221.—The trachea, showing perforation of an aneurysm of the aorta (from a specimen in the Museum of the Philadelphia Hospital).

channels is an early manifestation, and leads to passive congestion and often to dropsy and cyanosis. Necrosis of the parts which are directly compressed has already been alluded to. Portions of the clot within

the aneurysmal cavity not rarely become separated, and are carried as emboli to the peripheral parts of the circulation.

False or spurious aneurysms most commonly result from traumatism, though sometimes spontaneous rupture of the vessel is the immediate cause. The blood may find its way from the ruptured artery into the surrounding tissues, forming a blood-tumor, or *hematoma*, which becomes encapsulated by condensation of the surrounding tissues and by reactive overgrowth of connective tissue stimulated to activity by the fibrin formation and liberation of leukocytes. The retaining wall thus formed may in some cases be lined with endothelial cells, and secondary inflammatory thickening or atheromatous plates may form. When an artery and vein are both injured, as is sometimes the case in phlebotomy, the blood may enter the vein and distend this markedly. The term *aneurysmal varix* is applied to such cases. In other instances the artery

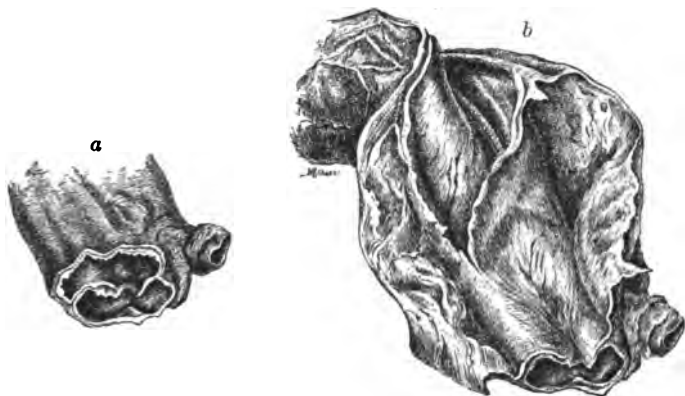


Fig. 222.—Dissecting aneurysm of the aorta: the aneurysm began near the aortic valves and extended to the iliac branches, converting the aorta into a double tube: a, Transverse section; b, longitudinal section.

and vein communicate by an intermediate sac formed by the condensation of the intervening tissues, and for such the name *varicose aneurysm* is used. Aneurysms may arise when by *erosion* of the adventitia and outer media the support of the vessel is so weakened that dilatation occurs in the direction of this lessened resistance.

THE VEINS

Anatomical Considerations.—The veins resemble the arteries, excepting that the muscular coat is less well developed, and that most of the veins are supplied with endothelial reduplications or folds, which act as valves and prevent the backward flow of the blood.

CIRCULATORY DISTURBANCES

Thrombosis of the veins is the most important condition. This, however, has been sufficiently considered under Thrombosis (see p. 67).

DEGENERATIONS

Fatty degeneration of the intima and media may occur as in the arteries, but it is comparatively rare and unimportant.

Calcification is met with in veins which have become dilated or varicose, or otherwise diseased.

INFLAMMATION, OR PHLEBITIS

Acute phlebitis is a comparatively common affection. It may occur as the result of inflammation, particularly of infectious nature, in the neighborhood of the vein. In such cases the outer coat is first involved, and the term "periphlebitis" is properly applied. This condition is met with in association with infected wounds and phlegmonous inflammations of the subcutaneous tissues. The veins beneath the skin may be distinctly visible as blue streaks running in various directions. Microscopically, there is found to be an invasion of the adventitia with round cells, and actual foci of suppuration are not uncommon. The cellular infiltration may extend to the media and some-

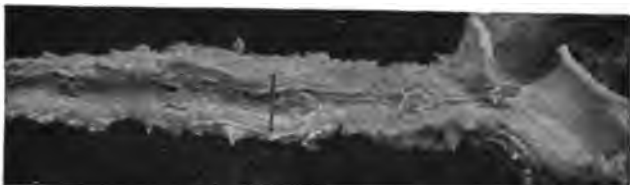


Fig. 223.—Thrombophlebitis of the femoral vein (from a specimen in the Museum of the Philadelphia Hospital).

times to the intima, and not rarely thrombosis occurs within. The thrombi thus formed may secondarily become infected, soften, and occasion septic embolism.

In another group of cases phlebitis begins from within, and is the consequence of primary thrombosis of the vein (Figs. 223 and 224). To such the name *thrombophlebitis* is applicable. The histological changes are similar in these to those which occur in thrombo-arteritis, and as terminal results localized thickening of the venous wall or irregular contractions by the formation of fibrous adhesions and even complete obliteration of the venous channel may result. When the thrombus is thus organized or partially organized calcification may eventually occur, and in this manner *phleboliths*, or vein-stones, are formed.

Chronic phlebitis, or phlebosclerosis, corresponds to chronic arteritis or arteriosclerosis. A certain amount of chronic inflammatory thickening of the vein ensues as a consequence of thrombophlebitis. Phlebosclerosis may also be due to overdistention of a vein resulting from thrombosis or other forms of obstruction, and thus plays a secondary part in dilatation of the veins, or phlebectasia.

Phlebosclerosis may, however, occur as a widespread affection in

association with arteriosclerosis, though rarely in equal degree, in consequence of certain systemic conditions—syphilis, alcohol, gout, etc. The changes occurring in the vein are much the same as those in the artery, but the new-formed fibrous tissue in the intima less commonly undergoes degenerative changes and calcification than in arterial sclerosis. Sections of the affected veins show, as a rule, absence of signs of inflammation and of marked degeneration. The essential change is a proliferation of the cells of the intima and of the connective tissue of the media. The condition resembles more a functional hyperplasia, the result of mechanical forces, than a chronic inflammation.

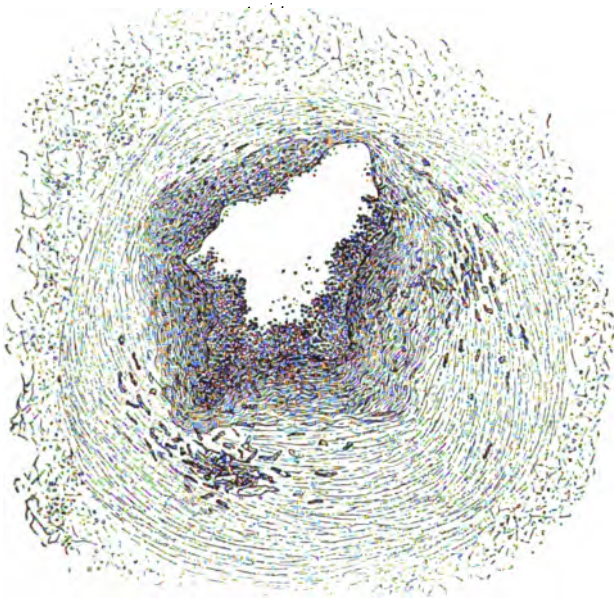


Fig. 224.—Phlebitis and periphlebitis of the umbilical vein of the newborn: purulent infiltration of the intima and adventitia; calcareous particles in the media (Birch-Hirschfeld).

In cases of congenital syphilis an interesting form of thickening of the intima, leading to stenosis or even complete obstruction, has been found in the veins of the umbilical cord, and less frequently in the portal vein. Similar hyperplastic endophlebitis has been found in the veins of the extremities in syphilis of adults.

DILATATION OF THE VEINS; PHLEBECTASIA; VARICOSITY

Etiology.—Dilatation of the veins occurs from mechanical obstruction to the circulation or from weakness of their walls. It presents itself more commonly in dependent portions of the body, and is particularly frequent in the veins of the legs, of the rectum, of the neck of the bladder, of the spermatic cord, of the scrotum, and of the vagina.

Mechanical causes are most important. Thus, in cases of cirrhosis of the liver, of obstinate constipation, and of pelvic tumors, dilatation of the veins of the rectum, causing hemorrhoids, is frequent. In cases of abdominal tumors, repeated pregnancy, or other causes of obstruction to the venous return of the blood from the lower extremities, varicosity of the veins of the legs is frequently observed. Always, however, local disease of the veins themselves tends to make the dilatations more pronounced, and, in addition, systemic depression and, particularly, cardiac weakness are contributing causes which operate by aiding in the stagnation of the blood, which otherwise might pass by collateral channels to its proper destination.

Pathological Anatomy.—The veins in phlebectasia become dilated and also elongated, so that they soon assume a tortuous character. Not rarely masses of much-dilated veins lie closely aggregated in groups or clumps beneath the surface of the skin; and communications may be established between the adjoining pouches of dilatation, and thus a cavernous tissue is formed. The walls of the dilated veins are usually considerably thickened (phlebosclerosis), and even calcification may occur in the intima.

Results.—The circulation of the blood is slowed and thrombosis is, therefore, frequent. The thrombi may undergo organization or calcification, or in other cases may soften and occasion embolism. When varicosities are established in the veins of any submucous tissue, catarrhal inflammation of the overlying mucosa is occasioned and generally proves obstinate. At the same time a certain amount of hyperplasia of the connective tissue between the dilated veins takes place and thickening of the mucous membrane results. When the subcutaneous veins are involved the skin is prone to become thickened and to present eczematous inflammation, while the subcutaneous tissue may be greatly increased in thickness and density (phlebectatic elephantiasis or pachydermia). Not rarely ulcerations of the skin of the lower extremity owe their origin to varicosity of the veins, and such ulcers are prone to prove indolent and obstinate. Hemorrhage may occur from varicosities of the submucous veins, particularly in case of hemorrhoids and in the esophageal varicosities of drunkards.

TUMORS

Tumors rarely begin in the walls of the veins, though myoma and sarcoma have been described. More commonly the walls of the veins are secondarily involved in cases of tumors surrounding them. Aschoff lays stress upon the involvement of veins by leukemic infiltrates and myeloma.

INFECTIOUS DISEASES

Tuberculosis not rarely attacks the veins, particularly those of the lungs. Perforation of the wall may take place, and miliary tuberculosis is a frequent consequence.

Syphilis of the veins has already been referred to.

THE LYMPHATIC CHANNELS

Anatomical Considerations.—The lymphatic system begins in the lymph-spaces, which are the spaces between the tissue elements in all parts of the body. These lymph-spaces unite to form definite lymphatic capillaries, which are channels having walls composed of a single layer of endothelial cells. The lymphatic capillaries unite to form larger vessels, and in these connective-tissue coats support the endothelial lining.

Lymph coagulates very slowly—ten to twenty minutes—due to the small amount of thrombokinase in it. Intralymphatic thrombosis does occur after ligation, but it is much favored by destruction of tissue locally, such a condition freeing thrombokinase. Opie has shown this by addition of tissue extracts to freshly drawn lymph. Bacterial invasion of lymph-channels assists in freeing thrombokinase.

INFLAMMATION

Inflammation of the lymphatic vessels, or lymphangitis, is always secondary to inflammatory affections of the parts surrounding the lymphatics, or of those parts from which the lymphatics take their origin. In cases of infective lesions of the extremities, red lines, indicating the position and course of the inflamed lymphatics, may not infrequently be seen beneath the skin, extending upward to the nearest lymphatic glands. Histologically, the first change in such cases is swelling and oftentimes multiplication of the endothelial cells of the lymphatic vessel; later, there may be accumulation of leukocytes within, and the lymphatic channel may be uniformly filled with pus or distended at different points. Usually a certain amount of perilymphangitis accompanies the process, and in cases of violent septic infection the surrounding tissues may become extensively involved in phlegmonous inflammation. Thrombosis may take place within the lymphatic channel in cases of moderate severity and thus obstruction ensue. The termination is either in resolution or suppuration, with more or less widespread involvement of the surrounding tissues. Resolution may be only partial, the inflammatory changes going on to the formation of connective tissue, which may obliterate the channels, or the restitution of the wall of the lymphatic vessel may be imperfect and subsequent dilatation results.

A primary chronic lymphangitis may arise from prolonged obstruction to the lymph flow or by continued irritation, as by foreign particles which the channels are draining to the lymph-nodes. The vessels are changed to a solid band of endothelial cells surrounded by a thickened fibrous coat.

DILATATION OF THE LYMPHATICS, OR LYMPHANGIECTASIA

This condition may be an acquired or a congenital affection.

Acquired dilatation of the lymphatics results from obstruction to the larger channels, as in cases of pressure upon or thrombosis of the

thoracic duct, or of obstruction of the lymphatic channels by filariæ. In other cases it is due to inflammations surrounding the lymphatics and leading to weakness of their walls. It is very commonly observed in the subcutaneous lymphatics, and constitutes the endemic elephantiasis of warmer countries. This condition is particularly common in the lower extremities, scrotum, and labia, but may affect other parts. The skin is greatly thickened and the surface often of irregularly lobulated character. On incision into it there is found an abundant exudation from the subcutaneous tissue of serous or of milky liquid.

Obstructive dilatation of the intra-abdominal lymphatics is not unusual. Rupture of dilated branches in the genito-urinary tract may lead to chyluria; similarly, chylous ascites or hydrothorax may arise by obstruction or rupture of the thoracic duct.

Congenital lymphangiectasia may take the form of a diffuse condition affecting the lymphatics more or less regularly in certain parts of the body, or it may appear in circumscribed areas, often in situations in which the ordinary lymphatic supply is not abundant. The diffuse form occasionally presents itself in the newborn in the form of edematous or semicystic swellings of the subcutaneous tissue, resembling those of elephantiasis. In the same group of cases belong the instances of congenital enlargement of the tongue (*macroglossia*) and of the lips (*macrocheilia*). In some of these instances the development of the condition does not occur until some time after birth, though the process is, in reality, congenital. Localized lymphatic dilatations constitute the form of new growth known as lymphangioma. (See General Pathology.)

INFECTIOUS DISEASES

Tuberculosis.—The lymphatics play an important part in the dissemination of tuberculosis within the organs, and they may themselves be involved in the disease. This is beautifully illustrated in cases of intestinal tuberculosis with ulceration. In such cases the lymphatic channels in the serous coat may be seen radiating from a point opposite the ulceration toward the mesentery, and small miliary nodules are seen in their course.

Syphilis.—The lymphatics may be involved in syphilitic processes in their vicinity, but the changes are not characteristic.

TUMORS

In addition to the lymphangiomata referred to, the lymphatic vessels are the primary seat of tumors resulting from multiplication of the lining endothelial cells, which are known as *endotheliomata*. These tumors are especially common in the serous surfaces, but may also be met with in the skin and elsewhere. The lymphatics bear an important relation to the metastasis of malignant tumors, particularly of carcinomata. The carcinoma cells enter the lymphatics and are carried by the stream to distant parts of the body; sometimes the lymphatics near carcinomata are found densely packed with cancer cells.

PARASITES

The adult of the *Filaria bancrofti* resides in the lymphatic vessels, and the embryos may be present in large numbers. (See General Pathology.)

THE THORACIC DUCT

Pathological processes involving the thoracic duct resemble in general character those of the other lymphatic vessels, but the size of the duct and its anatomical relations make the diseases affecting it of somewhat greater significance than the same diseases when occurring in the smaller lymphatics.

Thrombosis may occur in association with inflammation of the duct or without such, and there may be a permanent occlusion in consequence. Dilatation of the lower parts of the duct, as well as of the lymphatic vessels of the abdomen, may ensue, and sometimes the receptaculum or other portions of the duct may become cystic. Chylous ascites may likewise result. More commonly collateral circulation re-establishes communications and serious consequences are not observed.

Dilatation of the thoracic duct may also result directly from cardiac failure with engorgement of the greater veins. The outflow of lymph is impeded, and in some cases the backward pressure of the blood through the superior cava may fill and distend the upper part of the thoracic duct with blood.

Inflammation occurs in consequence of various inflammatory diseases of the abdomen or of the pelvis, by the invasion of irritants through the lymph received from the affected areas. There may also be direct extension of inflammation in cases of abdominal disease, or in pleurisy or other intrathoracic affections.

Tuberculosis affecting the abdominal portion of the duct is sometimes observed in cases of intestinal or mesenteric tuberculosis, and may occasion secondary miliary tuberculosis, particularly the form in which the disease is subacute or chronic in its course (Weigert). It occurs in periductal or intimal form. In the latter case it may be either as a soft spreading lesion leading to erosion and ulceration, or as a poly-poid outgrowth into the lumen.

Tumors.—Primary tumors (sarcoma, fibroma) are sometimes observed, and secondary carcinoma is more commonly met with.

CHAPTER IV

DISEASES OF THE RESPIRATORY SYSTEM

THE NASAL CAVITIES

Anatomical Considerations.—The mucous membrane of the nose is usually prominent, especially over the lower turbinated bone, where it is 4 mm. thick. In the lower or respiratory parts of the nose the epithelium is stratified, ciliated, columnar in type. The submucosa is replete with a venous network, giving it, particularly over the inferior turbinated bone, the appearance of erectile tissue. In the olfactory regions non-ciliated columnar cells, which become attenuated at the inner end, line the surface. Between the filiform prolongations within lie round and tapering *olfactory cells*. Small tubular and racemose serous and mucous glands are freely distributed in the mucosa.

CONGENITAL ABNORMALITIES

Deviations of the septum and other slight anomalies are common. Atresia, absence of the septum or other parts, or complete absence of the nose are rare defects. Harelip and cleft palate frequently involve the nasal cavities.

CIRCULATORY DISTURBANCES

Active hyperemia occurs in consequence of exposure to great heat or cold, or of ascending elevations, and when the heart is overstimulated. Certain odors or finely divided dust-particles may provoke transient congestion. Frequently, however, such congestion terminates in inflammation.

Passive hyperemia may be due to cardiac weakness, obstructive diseases of the lungs, and local pressure on veins.

Hemorrhage.—In either passive or active congestion and in inflammations of the mucous membrane hemorrhage (*epistaxis*) may occur. Bleeding may also result from blood-diseases (hemophilia, pernicious anemia, leukemia), from disease of the blood-vessels (arteriosclerosis), or in a paroxysmal form from obscure causes. Epistaxis is a frequent prodromal symptom of typhoid fever; less frequently it occurs in influenza and other infections. Trauma may cause nosebleed. It also may occur vicariously when normal menstruation fails.

Edema of the mucous membrane may be associated with inflammation.

INFLAMMATIONS

Acute nasal catarrh (acute rhinitis, coryza) commonly results from exposure to cold. Irritant fumes may cause it; often it seems infectious and contagious. It may occur as an associated condition in various infections, as grip, typhoid fever, measles, etc. Hay-fever and its related disorders are forms of acute rhinitis. Gout and other nutritional disorders may predispose to rhinitis or cause it. The mucosa is at first intensely red and dry; then an irritating serous, followed by mucous and finally mucopurulent, exudation is discharged. Herpes or eczematous eruptions of the lips are common. Considerable inflammatory edema of the mucous membrane of the nose and accessory cavities may occur. It may spread to the middle ear, to adjacent sinuses, or to the brain. This is especially true in the purulent form. Pyemia of the antrum of Highmore may start in this way.

Chronic rhinitis follows repeated acute attacks, especially in tuberculous or syphilitic persons. The mucosa, especially over the inferior turbinated bone, becomes thickened (*hypertrophic rhinitis*) and may remain so, or undergo atrophy (*rhinitis atrophica*). In the atrophic form the exudate is scanty and appears as dry, greenish crusts, which sometimes occasion extensive ulcerations and become horribly offensive. To such cases the term *ozena* is applied. Various forms of bacilli and micrococci have been discovered, the most frequent being an organism resembling the bacillus of Friedländer, which is considered the cause of the disease by many observers. Fetid discharges may also occur in syphilitic or tuberculous diseases of the nose (*ozæna syphilitica seu tuberculosa*).

In the hypertrophic variety the openings of the sinuses about the nose may be slowly closed, with resultant chronic inflammation, which may lead to widespread phlegmon or necrosis. In this form there is increase of the submucosa and but little change in the epithelial layer, except for occasional glandular distention or distortion of mucous glands. While secondary atrophy may occur, what is called atrophic rhinitis (as above described) is said by some to be atrophic from the start, there being atrophy of both glands and supporting tissue.

INFECTIOUS DISEASES

Diphtheritic rhinitis is usually secondary to pharyngeal diphtheria. Primary diphtheritic rhinitis of rather benign character is occasionally observed. Non-specific pseudomembranous rhinitis is a very rare condition.

Syphilis in the secondary stage and in congenital cases sometimes occasions simple catarrhal rhinitis. Mucous patches may occur, or gummata spring from the mucous membrane or from the periosteum or perichondrium. The latter tend to ulcerate and cause destruction. The purulent discharge may be fetid.

Tuberculosis may occur as disseminated or aggregated tubercles of the mucous membrane, or as ulcers and carious processes. These

are all rare, but "scrofulous catarrhs" of children, probably often due to tuberculous lesions, are common. *Lupus* of the face may extend to the nose.

Glanders occasions intense purulent and hemorrhagic rhinitis, or nodular growths with ulceration. Nodules and ulcers are common in *leprosy*. Irregular swelling and induration of the mucous membrane of the nose and the adjoining skin in *rhinoscleroma* are rare conditions.

TUMORS

The commonest form of tumor is the *polyp*, which is sometimes distinctly the result of hypertrophic rhinitis, at other times obscure in origin. Polypi present the ordinary structure of the nasal mucosa, with a tendency to cystic change from occlusion of the glands, or to adenomatous appearances from proliferation of the glandular elements. Fibroid, myxomatous, and sarcomatous polypi also occur. In all cases there is a tendency to recurrence after removal. A rare form of *hairly polyp* has been described. Chondromata, osteomata, sarcomata, and epithelial or glandular cancers may be found.

PARASITES AND FOREIGN BODIES

Larvæ of various flies may occur in the nasal chambers and set up serious inflammatory lesions. Foreign bodies may become incrustated with lime-salts and lead to the formation of *rhinoliths*. These formations may also arise around a nucleus of epithelial crusts, mucus, or desquamated epithelia in obscure niches of the nasal cavity after prolonged catarrh.

The *sinuses* (frontal, ethmoid, and sphenoid) and the *antrum of Highmore* are frequently involved in inflammations of the nasal mucosa, and when their outlets are obstructed by swelling of the nasal mucosa chronic lesions (catarrhal or suppurative) may occur. These may occasion generalized infections or infectious toxemias of various forms. Empyemata of the sinuses may open into the nose, the cranial cavity, the mouth, or may discharge externally.

THE LARYNX

Anatomical Considerations.—The lining epithelium of the larynx is stratified squamous as far as the false vocal cords. Below these and throughout the ventricles it is stratified, ciliated, columnar, and thus continues into the trachea and bronchi, excepting over the true vocal cords, which are covered with stratified squamous epithelium. The tunica propria contains much yellow elastic fiber, and the submucosa is quite loose, especially over the base of the epiglottis and the aryepiglottic folds.

CONGENITAL ABNORMALITIES

Minor defects in shape of the constituent parts of the larynx are not rare. Congenital fistulæ communicating with the exterior, and dilata-

tion of the ventricles similar to the normal pouching found in certain monkeys, are occasionally met with. Abnormal largeness and smallness, the latter especially in persons having poorly developed sexual organs and those castrated early in life, are more frequent conditions.

CIRCULATORY DISTURBANCES

Anemia may occur in general anemia, and is sometimes found in tuberculous and chlorotic subjects in pronounced degrees.

Active hyperemia follows exposure, overuse of the voice, and irritation by gases, dust, and the like.

Passive hyperemia occurs in heart diseases, intrathoracic tumor, and other conditions obstructing the venous circulation. In active congestion the larynx is bright red; in passive congestion it is dark red in color, and distended veins may be prominent.

Hemorrhages are seen in the mucosa after death from asphyxia, in cases of purpura or other hemorrhagic conditions, as well as in intense inflammation of the larynx. Large hemorrhages may occur in cases of cancer.

Edema of the epiglottis, the aryepiglottic folds, and other parts of the larynx may be part of anasarca in Bright's disease or heart disease, or may result from local pressure upon the veins. The parts become greatly swollen and of an anemic, translucent appearance. Great stenosis of the larynx commonly results. Generally "edema of the larynx" is inflammatory in nature (see below).

INFLAMMATIONS

Acute catarrhal laryngitis results from chemical or mechanical irritation; it accompanies whooping-cough, measles, small-pox, typhoid fever, and other infections. The mucous membrane is bright red and swollen. A scanty mucous or mucopurulent exudate is usually noted. Intense laryngitis is attended with small hemorrhagic ecchymoses or erosions; true ulcers are rare. Follicular ulcers are sometimes seen, and rarely small vesicles arise upon the surface (*herpetic laryngitis*).

As is the case with all surface inflammations, laryngitis may assume a catarrhal, fibrinous, pseudomembranous, purulent, or ulcerative form. They merge into one another and, with the exception of the specific forms, have no peculiar etiology or pathology.

Pathological Physiology.—Acute laryngitis may cause considerable disturbance of breathing by the swelling of the mucous membrane, and in children often leads to spasmodic contraction of the laryngeal muscles, with paroxysmal dyspnea (*false croup*).

Chronic catarrhal laryngitis may follow the acute form or begin gradually. Overuse of the voice and exposure to cold or irritating gases or dust are the common causes. The mucous membrane is usually thickened and somewhat granular or even papillomatous. There is a tendency for the epithelium to assume a squamous or epidermoid char-

acter (*pachydermia laryngis*). In the later stages atrophic changes may ensue. Fibrous thickening and stenosis of the larynx sometimes result from the chronic irritation of foreign bodies, such as intubation tubes.

Edematous laryngitis is generally known as *edema of the larynx*. Nearly always it is a true inflammatory edema, due to violent irritation, general or local infection, or severe local lesions of a chronic nature, such as tuberculous or syphilitic ulceration and perichondritis; it is also seen in angioneurotic edema. The looser submucous tissues at the base of the epiglottis and over the aryepiglottic folds become greatly swollen, and the surface is more or less translucent. Sometimes the edematous infiltration is yellowish, or even quite purulent, especially in cases in which phlegmonous suppurations have extended from neighboring parts (retropharyngeal abscess, erysipelas). When circumscribed areas are affected *abscess* results.

Perichondritis, inflammation of the perichondrium of the cartilages of the larynx, is usually secondary to serious laryngeal diseases, as syphilitic or tuberculous ulcers, carcinoma, etc. It may be primary in typhoid fever or other infections. Frequently suppuration and necrosis of the cartilage result, but merely localized induration and swelling may occur.

INFECTIOUS DISEASES

Diphtheritic and croupous inflammations may be part of the anatomical changes in diphtheria, but may also occur in typhoid fever, scarlet fever, small-pox, or other infectious diseases (due in such cases to streptococci or other organisms), or from violent irritation by steam or the like. The surface of the larynx is covered with a more or less adherent grayish or yellowish pseudomembrane, which consists of a network or masses of fibrin entangling degenerated round cells and epithelium. The membrane is most adherent where the epithelium is squamous. Diphtheritic laryngitis usually follows a similar process in the pharynx. (See Diphtheria and Pseudomembranous Inflammation, Part I, page 131.)

Tuberculosis is nearly always secondary to pulmonary tuberculosis; primary lesions are exceedingly rare. Small localized tuberculous masses or more diffuse tuberculous infiltration are found in the mucosa and submucosa, especially on the posterior wall of the larynx, and may remain for long periods as the infiltrative type, but caseation and ulceration are usually early developments (Fig. 225). There is no reason to divide the tuberculous lesions in the larynx into different forms, as they do not have peculiar courses. Simple catarrhal inflammation or hypertrophic conditions of the mucous membrane between the tuberculous masses, giving rise to warty or polypoid growths or edematous laryngitis and perichondritis, may complicate the tuberculous lesions. *Lupus* of the nose and pharynx may extend to the larynx, where it occasions nodular thickenings and ulceration. Primary laryngeal lupus has been observed.

Syphilis may occasion simple catarrh of the larynx, mucous patches, or infiltration and erosion of the mucous membrane secondary to pharyngeal involvement. The latter conditions are most frequent in the epiglottis, the posterior wall of the larynx, and the vocal cords. Gumata may occur in the same situations independent of pharyngeal syphilis, and lead to deeper ulcers. In the healing of syphilitic ulcers irregular papillomatous elevations of the healthy mucosa or extreme contractions and deformities of the larynx may occur.

Lepra and **glanders** sometimes occur in the form of nodular swellings and ulcers.

Swelling and ulceration of the lymphatic follicles, chiefly at the base and side of the epiglottis, analogous to the lesions in the intestines, may occur in *typhoid fever*; and in *small-pox* there may be small areas of infiltration and epithelial degeneration, or even pseudomembranes.

Atrophy of the mucous membranes with various degenerative changes or deposits may occur in the larynx as the result of chronic inflammation *in loco*, or as a part of a constitutional disease (gout, rheumatism).

Stenosis is due to pressure from without or by contraction of healed ulcers.



Fig. 225.—Tuberculous erosion and ulceration of the larynx, causing extensive destruction of the vocal cords (from a specimen in the Museum of the Philadelphia Hospital).

TUMORS

Papilloma.—Over one-half of all tumors of the larynx belong to the group of *papillomata* or *papillomatous fibromata*. These are simply hypertrophied papillæ covered with a thick mantle of squamous epithelium (Fig. 226). The stroma may be insignificant and the epithelium considerable (hard papilloma), or the stroma may be excessive, highly vascular, and infiltrated with round cells, while the epithelial covering is thin (soft papilloma). Papillomata are most frequent on the false vocal cords or on the other parts of the larynx lined with squamous epithelium. They usually occur in numbers, but may be solitary. Chronic inflammation often determines their occurrence, and they are not infrequent around chronic ulcers or carcinoma of the larynx. Simple hyperplasia of mucous membrane, of normal structure, occurs in various chronic inflammatory conditions of the larynx.

Fibroma.—Nodular, sessile, or polypoid fibromata constitute one-third of all tumors. They are most frequent on the vocal cords and in the upper part of the larynx.



Fig. 226.—Papillomata of the vocal cords (from a specimen in the Museum of the Philadelphia Hospital).

Cystic dilatation of the glands may occasion *mucous polypi*. Adenoma, lipoma, myxoma, sarcoma, and chondroma are rare tumors. Tumor-like masses of heterotopic thyroid-gland tissue have been found in the larynx.

Carcinoma may be primary or, less frequently, secondary. Primary carcinoma is usually of the squamous variety and occurs about the vocal cords. Nodular thickening with ulceration results. Papillomatous thickening of the mucous membrane frequently surrounds the growth. Secondary involvement of the cervical glands and esophagus may occur.

Of 1100 tumors of the larynx collected by Bruns, 602 were papillomata; 346, fibromata; 73, mucous polyps; and 27, cysts; 76 per cent. occupied the true cords or the anterior commissure of the cords. Mackenzie found 67 per cent. papillomata and 16 per cent. fibromata.

PARASITES AND FOREIGN BODIES

The larval *Trichinella spiralis* may infest the laryngeal muscles; and *lumbricoids* occasionally enter from the pharynx. *Echinococcus* cysts are very rare.

Large foreign bodies may cause death by suffocation. Smaller bodies may rest in the larynx, especially the ventricles, for years, becoming surrounded by hyperplastic mucous membrane or a capsule of fibrous tissue. Calcareous concretions may form around small foreign bodies or spontaneously in the ventricles.

THE TRACHEA

MALFORMATIONS

Congenital Malformations.—Complete absence of the trachea occurs in acephalic monsters. Congenital decrease in length or diameter, in the number or completeness of the cartilages, and similar minor deformities are more common. An adventitious bronchus is occasionally seen, especially on the right side, and fistulous communications with the exterior or with the esophagus are rare congenital defects. Diverticula may be due to a rudimentary condition of a supernumerary bronchus. Congenital cysts may occur between the trachea and esophagus when fistulous communications between them become closed at either end.

Acquired Malformations.—Dilatations of the trachea may be diffuse or localized. They depend for their occurrence upon weakness of the walls and some impediment to expiration. Saccular dilatations are usually on the posterior wall. Narrowing of the lumen may be due to pressure of tumors or aneurysms, to new growths or cicatricial contractions (especially syphilitic), or to foreign bodies within.

CIRCULATORY DISTURBANCES

Anemia and active and passive congestion result from the same causes as in the larynx, and the pathological anatomy is the same.

INFLAMMATIONS

Inflammations are usually associated with laryngitis or bronchitis, and are due to the same causes. Simple catarrhal and pseudomembranous inflammations are met with. Foreign bodies may cause extensive and deep inflammation, leading to ulceration and sometimes perforation. Chronic inflammation assumes a proliferative and, later, an atrophic character. Proliferative (polypoid) inflammation is not infrequent after tracheotomy, and may occasion serious obstruction. Ozena of the trachea may be associated with nasal ozena.

INFECTIOUS DISEASES

Tuberculosis and **syphilis** occur under the same circumstances as in the larynx. Syphilis may, however, affect the trachea and bronchi independent of disease of the pharynx or larynx.

TUMORS

Primary tumors are rare. Secondary involvement by *cancer*, extending from the esophagus or thyroid gland, or by *sarcoma*, from the surrounding lymphatic structures or thymus gland, is more frequent. *Ecchondroses* and *osteomata* may spring from the cartilages, and multiple *chondromata* have been found in the mucous membrane. Retention-cysts of the mucous glands are occasionally seen on the posterior wall, protruding outside the trachea.

THE BRONCHI

Anatomical Considerations.—The larger bronchi correspond very closely to the trachea in structure. The smaller divisions have thinner walls, being less provided with cartilaginous rings, but having instead small cartilage-plates and a greater abundance of muscle-fibers. The tubes having a diameter less than 1 mm. are called the *terminal bronchioles*, and lead into yet smaller tubes, the *alveolar passages*, which open into dilated *infundibula*, and the last named are finally surrounded by

air-sacs. The lining epithelium is stratified columnar ciliated down to the terminal bronchioles, where it becomes simple columnar. In the alveolar passages there is first polygonal, then flat, epithelium; while in the infundibula and air-sacs there are practically only flat epithelial cells.

CONGENITAL MALFORMATIONS

These are rare and unimportant. Dilatations or narrowing and anomalous division of the tubes have been noted. (See Trachea.)

CIRCULATORY DISTURBANCES

Anemia and hyperemia occur under the same circumstances as in the trachea and larynx.

Hemorrhage.—Intense congestion may occasion hemorrhages into the mucous membrane or into the bronchi themselves. More frequently hemorrhage is due to catarrhal inflammation, tuberculous ulceration, or a general hemorrhagic tendency. Aneurysms of the aorta (see Fig. 220) and the small aneurysms of the pulmonary arterioles in tuberculosis of the lungs not infrequently rupture through the bronchi.

INFLAMMATIONS

Both acute and chronic bronchitis are common conditions, and there are several forms.

Acute catarrhal bronchitis results from exposure, from inhalation of irritating gases, and from downward extension of tracheal catarrhs. The terminal bronchioles are frequently affected secondarily in pulmonary diseases. Bronchitis is constantly associated with some of the infectious fevers—typhoid fever, measles, whooping-cough, etc. Various micro-organisms have been found in bronchitis. Among these are the pyogenic micrococci, the diplococcus of Fränkel, the bacillus of Friedländer, the *Bacillus influenzae*, the *B. coli*, with many others. The mucous membrane presents an intensely red color; at first it is dry, but later a mucous or mucopurulent exudate is formed (see Fig. 32). The exudation may be excessive in quantity, in which case the condition is called *bronchorrhea*. This may be serous or purulent, and is sometimes very offensive in odor (*fetid bronchitis*).

Accordingly, as the exudate assumes a serous, mucous or mucopurulent, or fibrinous character, these names are applied. They have no etiological significance aside from the specific infections. All forms may go over into gangrenous bronchitis by retention and putrefaction of exudate.

Microscopically, the bronchial mucous membrane is infiltrated with round cells, especially in the purulent cases; the epithelial cells are degenerated, many being converted into goblet-cells; and the mucous glands are distended with mucus. The mucosa of the bronchi is covered with mucopurulent material containing degenerated epithelial cells and

detritus. The inflammatory conditions may extend outward as far as the peribronchial tissue, and occasionally there is some perichondritis.

Capillary bronchitis is a form confined, at least in the early stages, to the finest bronchioles, and it may go over into a catarrhal pneumonitis.

Pathological Physiology.—Bronchitis may occasion no other disturbance than cough. In many cases, however, the infection may cause fever and general depression. Substernal soreness or pain is not infrequent, while generalized thoracic pain may result from the violent coughing. Dyspnea is rare excepting in children and old persons, in whom cardiac weakness and spasmodic contractions of the bronchi seem to be operative.

Chronic catarrhal bronchitis occurs after repeated attacks of the acute form, and especially in old persons or in those who have some cardiac weakness which tends to cause congestion of the bronchi.

Gout seems to constitute a distinctly predisposing cause. Chronic bronchitis is frequently associated with chronic diseases of the lungs. In chronic cases the mucous membrane may undergo considerable alteration. Frequently the ciliated cells disappear entirely and are replaced by columnar or polygonal epithelium; and hypertrophic conditions of the mucous membrane are sometimes present. More frequently the bronchus is uniformly thickened by cellular infiltration and overgrowth of fibrous tissue. It may, indeed, become hypertrophic, and when the overgrowth encroaches upon the lumen with progressive granulation tissue an obliterating bronchitis occurs. The



Fig. 227.—Large bronchial coagulum; chronic fibrinous bronchitis (Vierordt).

exudate in chronic bronchitis is purulent and is accompanied by disarrangement and alterations in the bronchial epithelia.

Fibrinous bronchitis occurs under a variety of conditions. It is most frequent in association with laryngeal and tracheal diphtheria, but may also be due to inhalation of powerful irritants. Fibrinous inflammation of the finer bronchi occurs in both croupous and catarrhal pneumonia. Finally, there is a form of chronic or essential fibrinous bronchitis, characterized by periodic attacks, in which fibrinous casts of the bronchi are formed and discharged (Fig. 227). In all forms of fibrinous bronchitis there are often found in the sputa, on microscopical examination, fine spirals wound about a central fiber (*Curschmann's spirals*); and within these or associated with them the small octahedral crystals described by *Charcot* and *Leyden* (Fig. 228).

Bronchiolitis Exudativa.—This term was given by Curschmann to the condition of the terminal bronchioles he assumed to be present in cases of asthma. The sputa contain the spirals that bear his name and Charcot-Leyden crystals. The sputa in these cases are further characterized by the abundance of eosinophile cells (Figs. 228 and 229).



Fig. 228.—Sputum from a case of asthma, showing Curschmann spirals, Charcot-Leyden crystals, leukocytes, and numerous free eosinophile granules; unstained specimen (Jakob).

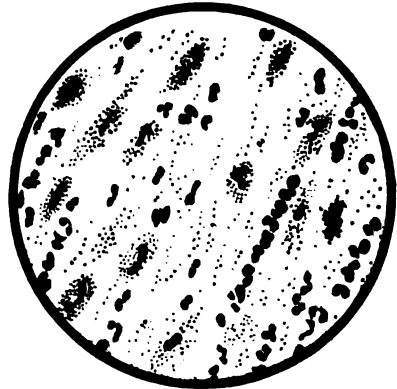


Fig. 229.—Sputum from a case of asthma, showing leukocytes, some containing eosinophile granules, free eosinophile granules, and micrococci; stained with eosin and methylene-blue (Jakob).

Ulcers of the bronchi are met with in severe catarrhal inflammations, but more frequently are tuberculous, syphilitic, or due to extension of ulcerative processes from neighboring parts. It is not unusual to find ulceration in the main bronchus opposite the point of pressure of an aneurysm.

Peribronchitis may occur from direct extension of inflammation from within, or it may be due to extension along the lymphatic channels from the pleura or interlobular septa of the lung. It is found most frequently as a part of pulmonary tuberculosis, and may be fibrous, caseous, or purulent.

STENOSIS AND OBSTRUCTION OF THE BRONCHI

The smaller bronchial tubes may be considerably occluded by catarrhal swelling of the mucosa and accumulation of exudate within. Clinically, this is often so marked in bronchitis affecting the terminal bronchioles as to have suggested the name "suffocative catarrh." (This capillary bronchitis is always merely a part of bronchopneumonia, and will be considered under that head.) More serious obstructions of the bronchi occur when old ulcers have healed, leaving cicatrices; or in cases of tumors of the bronchi or pressure upon the outside. If the obstruction be total and permanent, atelectasis of the lung occurs in that part supplied by the affected tubes. In temporary obstruction a mild

local emphysema occurs beyond the obstruction. Foreign bodies are usually coughed up, but may remain for long periods and occasion obstruction.

BRONCHIECTASIS, OR DILATATION OF THE BRONCHI

This is due to increased pressure within the bronchi or to some weakness of the walls, or to both, when the fault lies primarily in the bronchial walls. The weakening of the walls is most frequently due to chronic bronchitis. If it is extreme, simply the force of the inspired air may suffice to cause dilatation, but the increased expiratory efforts of coughing may aid materially. When a part of the lung is collapsed (atelectasis) the impediment to the entrance of air leads to dilatations of the bronchi above the collapsed area. This is especially noted in children. The weight of accumulating secretions in the tubes is an occasional cause of bronchiectasis. Finally, in fibrous pneumonia the traction of the connective tissue, attaching itself, on the one hand, to the outer wall of the bronchus, and, on the other hand, to the pleura, may bring about considerable dilatations.

An analysis of series of cases shows that chronic bronchitis and chronic cough stand at the head of the etiological antecedents. Probably in a much larger proportion of cases than is now recognized there is an association of bronchial dilatation with chronic bronchitis. The clinician and pathologist also have in the past given little attention to cases in which the dilatations were not pronounced or saccular. Clinically, there can, however, be recognized a group of cases of chronic bronchitis with excessive sputa in which the bronchi are probably uniformly though slightly dilated.

Among the other causes tabulated are preceding pneumonia, pleurisy, tumor, foreign body in the bronchus, aneurysm.

A congenital varicose dilatation of bronchi is sometimes seen.

The enlargement of the bronchus may be localized, when it is termed *saccular bronchiectasis*; or more uniform, when the names *cylindrical* and *fusiform* are applied, according to the shape of the bronchus (Fig. 230). The mucous membrane may be almost normal in ap-

pearance in small dilatations, but more commonly is thickened and irregular on the surface. There may even be actual polypoid outgrowths, and ulcerations may occur when the secretions are specially abundant and irritating. Microscopically, the epithelium is found to approach the squamous type; the wall of the bronchus is generally infiltrated and cirrhotic. The exudation is generally purulent and copious, and may be very fetid. Occasionally it is thick and cheesy.

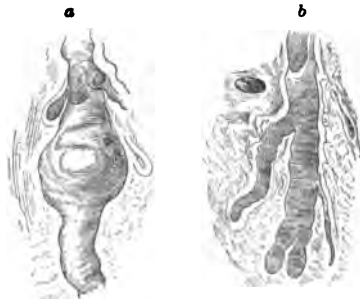


Fig. 230.—Bronchiectasis: *a*, Saccular; *b*, cylindrical; one-half natural size (Orth).

Bronchiolectasis.—Cases of extensive dilatation of the small bronchi and bronchioles have been observed. They are especially common in childhood and may be of a bronchitic type when bronchitis is the precedent condition, and an obscure pneumonic form in which the bronchiolar dilatation is associated with pneumonic consolidation.



Fig. 231.—Honey-comb lung, illustrating the extreme results of generalized acute bronchiolectasis of the bronchitic type (H. Morley Fletcher's case).

Bronchiolitis may be acute or chronic in its course and localized or quite general. In some cases the lung is quite honey-combed in appearance (Fig. 231).

INFECTIOUS DISEASES

Tuberculosis of the bronchi is usually associated with pulmonary tuberculosis, and appears in the form of miliary or larger nodules in the mucosa or submucosa, which tend to break down to form ulcers.

Syphilis sometimes occurs in the form of eruptions and ulcers. There may be dense scar formation and deformity in consequence of the healing of such ulcers.

TUMORS

Polypoid conditions of the mucosa occur in cases of chronic bronchitis. Fibroma, chondroma, and lipoma are rare forms of tumors. Pri-

many cancers may spring from the mucous glands or from the surface epithelium, but are very rare. Leukemic nodules are seen in the bronchi at times, and lymphosarcomata are not rarely found to spring from the peribronchial lymphatic tissues.

PARASITES AND FOREIGN BODIES

Bronchiectatic cavities may contain a growth of *aspergillus—mycosis aspergillina*. Round worms may enter by migration, and hydatid cysts are met with. The *Paragonimus westermanii* is a rare parasite invading the bronchi.

Foreign bodies from the exterior usually enter the right bronchus. They often lead to serious inflammation and suppuration, unless they are coughed up. Bronchial concretions sometimes form by inspissation of the secretions, especially in bronchiectatic cavities. Very rarely cartilaginous or bony masses, derived by outgrowth and later separation from the bronchial cartilages, are observed.

THE LUNGS

Anatomical Considerations.—The structure of the lungs in their unexpanded condition is very similar to that of an epithelial gland, consisting of ducts, the bronchi; and glandular tissue, the pulmonary parenchyma. The terminal bronchioles divide into several alveolar passages, which open into infundibula, and these, in turn, are surrounded by air-sacs. The groups of infundibula connected with a terminal bronchiole constitute an acinus. Neighboring acini unite to form lobules, and the lobules unite to form lobes. The epithelial lining cells of the air-sacs are large flat plates, which resemble endothelial cells very closely. Beneath these cells is a layer of elastic tissue, which gives the lungs their characteristic elasticity, and in which is embedded a rich network of capillaries, that carry on the proper respiratory function of the lungs. These capillaries are the terminal ends of the pulmonary artery. Another set of blood-vessels, the bronchial arteries, serve only to nourish the walls of the bronchi and the structure of the lungs themselves. The return circulation is mainly carried on by the pulmonary veins, which receive the blood of the pulmonary arteries and much of that of the bronchial arteries. The distribution of the lymphatic vessels in the lungs is of the greatest significance in pathological anatomy, especially with regard to the dissemination of infectious diseases in the lung itself. One system of lymphatics begins in the lymph-spaces between the cells of the intervesicular septa. These lymph-spaces deliver their contents to lymphatic capillaries in the same region, and these, in turn, follow the alveolar passages, surrounding the latter on all sides. Where the several alveolar passages unite to form a terminal bronchiole the smaller lymphatic capillaries also unite to form larger branches, which follow the bronchioles. Other lymphatic vessels surround the pulmonary veins, constituting a perivascular system. Still another

system begins in small subpleural capillaries, which unite, enlarge, and then penetrate the lung along the interlobular septa. Some of them, however, pass at once to the peribronchial and perivesicular tissues. All the lymphatic trunks leave the lung at the root and eventually discharge into the thoracic duct.

Collections of lymphoid cells are found in various places along the lymphatics in the tissue of the lung. Near the root these are of considerable size, and merit the name of lymphatic nodes or glands. Still larger and more important ones are found surrounding the bronchi just outside the lungs and around the end of the trachea.

CONGENITAL DEFECTS

Complete absence of the lungs has been noted in certain monsters. One lung may be absent, or its parenchyma may be undeveloped, while the bronchi are dilated even to a cystic condition. The opposite lung is compensatorily enlarged. Minor abnormalities in the division of the lobes and the like are not rare; and in a few instances accessory lobes, wholly disconnected from the rest of the lung, have been observed.

CIRCULATORY DISTURBANCES

Anemia of the lung occurs as a part of general anemia, from pressure upon the lung, or from obstruction or obliteration of the blood-vessels. The last is the cause of the great pulmonary anemia in emphysema of the lungs. The lungs are pale in color or of a mottled appearance in elderly persons, in whose organs considerable pigment is usually present. The apex is the first part to show anemia.

Active Hyperemia or Congestion.—Exercise constantly leads to increased flow of blood to the lungs, and this may be extreme, causing rapid death (*apoplexia pulmonum vascularis*). In cases of irritation of the lungs by the inhalation of heated or cold air, or of irritating gases, and in certain lesions of the base of the brain there may be more or less active congestion of the lungs (Fig. 232). *Collateral hyperemia* occurs when the opposite lung or some other part of the body becomes anemic through a stoppage of the circulation in that part. The lung in active hyperemia has a dark-red color, and on section blood flows from the surface of section. The alveoli may contain free blood, and in marked cases there is blood in the sputa during life.

Passive hyperemia is, for the most part, a chronic condition due to causes which prevent the outflow of blood from the lungs. The most frequent cause is valvular disease, particularly mitral stenosis and regurgitation; but weakness of the left ventricle from fatty disease or fibroid degeneration acts in a similar manner. Any local cause of hindrance to the outflow of the blood in the veins leads to similar passive congestion. It is often found in the dependent parts of the lungs in cases of great asthenia, as in typhoid fever, when the respiratory movements are ineffectual in properly emptying the pulmonary vessels.

This is called *hypostatic congestion*; not infrequently it leads to hypostatic pneumonia when irritants are inspired or descend through the bronchi to the parts of the lung affected. Postmortem there is often a similar hypostatic congestion, but without any evidences of catarrhal

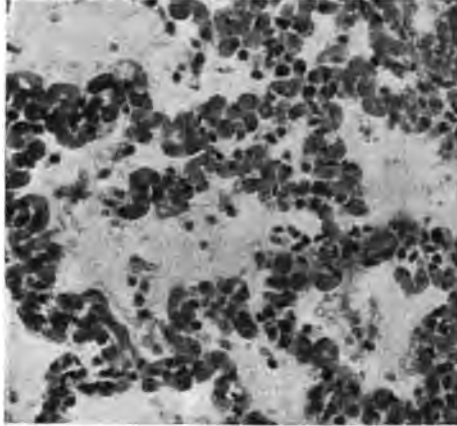


Fig. 232.—Acute congestion of the lung (Karg and Schmorl).

inflammation of the bronchi, such as always occurs in the cases developed during life.

The lung in passive hyperemia is dark-red in color and heavy. In the more acute cases it is moist on section, being infiltrated with serous



Fig. 233.—Phagocytic cells of the sputum, containing blood-pigment, from a case of cardiac congestion of the lungs (Jakob).

exudate and blood; in chronic cases, as in slow heart-failure, the tissue is dry and indurated. Microscopically, the blood-vessels in the alveolar walls are seen to be greatly distended, irregular, tortuous, and project into the alveoli. Red and white blood-corpuscles are seen within

the alveoli and in the interstitial tissues. In the later stages the red corpuscles either re-enter the circulation or break down to form dark pigment-granules within the alveolar epithelial cells, the leukocytes, or lying free in the tissues of the alveolar walls. In such cases there are at the same time considerable hyperplasia and induration of the connective tissue of the lung; and the whole process is called *cyanotic induration*. In cases of heart disease with congestion of the lungs there are very commonly found in the sputa pigmented epithelial cells and leukocytes, such as those described above (Fig. 233). These have been called heart-failure cells (*Herzfehlerzellen*). They are of some diagnostic importance.

Edema occurs most frequently as a result of passive hyperemia and is due to disproportion in the expulsive force of the two ventricles. The acute edema of nephritis may possibly be due to the inability of the left heart to empty because of the continued circulatory hypertension. In other cases the edema is the consequence of general septic conditions which lead to unusual permeability of the blood-vessels. In this group of cases belong the instances of "acute idiopathic edema" which are apparently independent of cardiac weakness and probably dependent on some form of infection. This is sometimes seen as an acute fatal attack in persons suffering from vascular disease, especially of the aorta, and in nephritics. Similar edema, not dependent on passive congestion, occurs in the parts of the lung surrounding inflammatory areas, and in some cases sudden pulmonary edema seems dependent on vasomotor relaxation. In cases of stenosis of the larynx, edema of the lung may result from the reduced pressure of air in the alveoli and the consequent suction of blood to the pulmonary circulation. In the cases of edema due to passive congestion the lungs are dark-red in color, firmer than normal, pit on pressure, do not show normal crepitation, and on section more or less serous fluid, rendered frothy by admixture of air, exudes from the cut surface. In long-standing cases the exuding fluid may be dark by admixture of degenerated blood. In the other forms of edema the lung may be quite light in color, generally grayish, but on section the same frothy serum exudes from the surface.

Microscopically, little is to be seen. There is some congestion of the septa, with a few epithelial cells and a hyaline coagulum in the alveoli.

Hemorrhage.—Small punctate hemorrhages occur in cases of severe congestion or inflammation, in the hemorrhagic or infectious diseases, and in consequence of high blood-pressure, as in death from asphyxia or in whooping-cough. The cause of such hemorrhages is inflammatory or degenerative weakening of the vessel walls or an obstruction of the lumen. When the former exists, and the latter supervenes, the production of hemorrhage is easier and more extensive. When hemorrhage from congestion is combined with serous effusion the lung assumes an appearance not unlike that of a hyperemic spleen (splenization). A form of apparent hemorrhage is seen in cases in which the blood is aspirated from the bronchi. In such cases lobular spots of hemorrhagic infiltration are found at the bases. Large hemorrhages into the substance of the lungs may be

traumatic, or they may be due to rupture of an adjacent aneurysm into the lung. Small or large pulmonary hemorrhages are at times due to lesions of the nervous system, especially of the base of the brain.

Hemorrhage from the lungs, discharging externally through the bronchial tubes, is most commonly due to tuberculosis, and is particularly frequent in the late stages, when cavities have formed. The immediate source of the bleeding is generally an eroded vessel in the wall of the cavity, and a small miliary aneurysm is commonly found at the point of erosion. Hemoptysis may be the first indication of the existence of pulmonary tuberculosis, but the old belief that hemorrhages cause phthisis is ill founded. A hemorrhage or any other lesion of the lungs may, of course, add to the liability to infection; but, as a rule, the cases in question are instances of hemorrhage occurring before the other evidences of the pulmonary disease have become marked. Occasionally, hemoptysis is due to congestion of the lungs, to erosion of small blood-vessels from gangrene, abscess or the like, or to vicarious menstruation.

Hemorrhagic infarcts may occur in the lungs, as in other places, from obstruction of the arteries by emboli. The latter come from the right heart or from the general venous system, and lodge in the smaller branches of the pulmonary artery, frequently at their points of subdivision. Very often, however, emboli are not found, or, if so, are so small as to have been unable to cause obstruction without the associated thrombosis, or there may be purely thrombotic occlusion. Valvular lesions and muscular weakness of the heart aid greatly in the production of infarctions by causing a sluggish circulation in the pulmonary vessels, and thus encouraging thrombosis. Infarctions are occasionally due to thrombosis of the pulmonary veins without obstruction of the arteries; more rarely they are caused by occlusion of one of the bronchial tubes. The latter condition leads to collapse (*atelectasis*) of the part of the lung associated with that tube, to consequent congestion (see *Atelectasis*), and, sometimes, when the congestion is severe, to hemorrhage. In addition, it is to be remembered that hemorrhages into the lungs are likely to have the shape and appearances of ordinary infarcts, because they occupy the area supplied by the bronchus into which the blood finds its way. Contributory causes are to be found in emphysematous lungs or those with senile or chronically altered arteries. These act as conditions favoring embolism and, secondarily, thrombosis by reason of degenerated vessel walls, and a loss of accommodative power by the pulmonary vascular and tissue tension. Infarctions are most frequently found in the lower lobes and in the right lung; they are usually multiple (Fig. 234) and have the characteristic wedge shape, the base of the wedge directed toward the pleural surface. They are hard, airless, dark colored, and project above the other parts on section and on the pleural surface. The pleural surface is at first shining and dry; later it becomes moist, then cloudy, and a layer of lymph appears, sometimes to be followed by a distinct fibrinous or adhesive pleuritis. Microscopically, there is seen a uniform hemorrhagic infiltration of the tissues (Fig. 235) and not infrequently hyaline thrombosis of the smaller blood-vessels.

Toward the apex of the infarct there is more fibrin in the blood-vessels, and the main vessel may be found obstructed by an embolus or thrombus. Small infarcts may be wholly removed through the vascular and lymphatic channels after liquefaction and granular degeneration of the

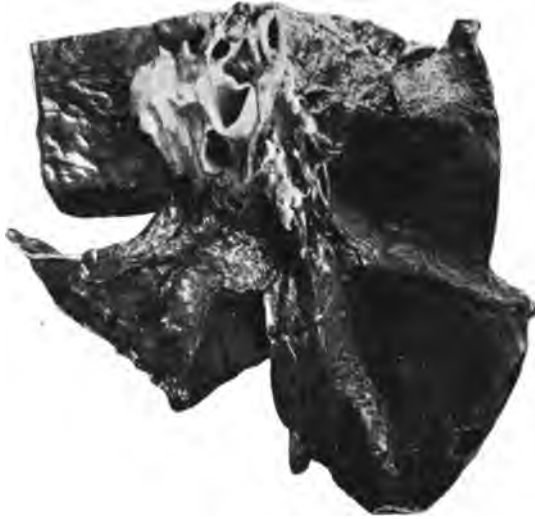


Fig. 234.—Double hemorrhagic infarct of lung (from a specimen in the collection of Dr. Allen J. Smith).

blood-clot. More commonly a pigmented scar is left. Softening and cyst formation may occur, or in cases in which the original embolus was infected by micro-organisms, or in which the infarct becomes infected through the bronchial tubes, abscess or gangrene may result.

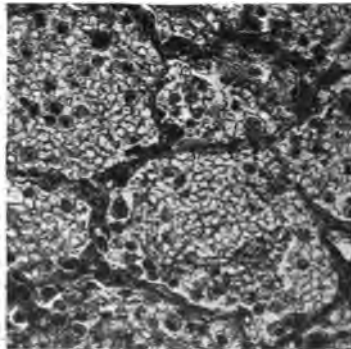


Fig. 235.—Hemorrhagic infarction of the lung (from a photograph by Dr. Wm. M. Gray).

Embolism without infarction is not infrequent in the lungs. An interesting form is fat-embolism, resulting from fracture of a bone with disorganization of the marrow, and less frequently from traumatic disturbances of other fat tissues. When large branches of the pulmonary

artery are occluded in this way, or when numerous vessels are obstructed, sudden death may result. In other cases there are merely great dyspnea and oppression. Air-embolism, embolism of hydatid cysts and of portions of tumors are rare. Attention has been called to the embolism of placental cells in certain cases of eclampsia.

HYPERTROPHY AND ATROPHY

Hypertrophy.—True hypertrophy, in the sense of increase of all the constituents of the lung tissue, is extremely rare, and probably only occurs when areas of the pulmonary tissue have been rendered useless early in infancy or in fetal life. Cases have been observed, however, in which a single lung occupied the entire side of the thorax to which it belonged, and also a part of the other side, where complete atrophy of the other lung had existed. It may be that limited areas of hypertrophy occur more frequently than we at present believe, but evidence is wanting.

Partial Hypertrophy.—The muscular tissue of the intervesicular septa and of the smaller bronchioles not infrequently undergoes proliferation or hyperplasia when there has been obstruction in the air-passages, so that greater expiratory force was required. Similarly, the elastic tissues may become increased; but these are not instances of true hypertrophy.

Atrophy.—Aside from that which occurs as a part of emphysema, atrophy does not take place.

EMPHYSEMA

By this term is indicated an increase of the air contained within the lungs, either in the normal tubes and alveoli or in the interstitial connective tissue. Two varieties of emphysema may be distinguished by their essentially different nature. These are the *interstitial* and the *vesicular*.

Interstitial emphysema of the lungs is similar to the emphysema of the subcutaneous tissues—*i. e.*, the term refers to the existence of air within the fibrous tissue of the lung. This occurs in the course of affections in which there is some obstruction to the expiration, combined with severe coughing or forcible expiratory efforts, leading to rupture of the intervesicular septa and extravasation of air. Degenerative or inflammatory weakness of any part of the pulmonary structure would, of course, act as a primary cause. Interstitial emphysema is most commonly observed in such diseases as whooping-cough and membranous croup; it may also result simply from straining efforts, as in women during labor, or from forcibly blowing wind-instruments, etc. The air from the ruptured air-vesicle finds its way into the interalveolar and intervesicular septa, and, passing along these, eventually reaches the interlobular and subpleural connective tissue, where it is seen in the form of small blebs, movable from place to place. The process may extend to

the roots of the lungs, and even to the mediastinal tissues or to the subcutaneous tissues of the neck. When an air-vesicle near the pleural surface ruptures, pneumothorax may result.

Vesicular emphysema is the term used to designate overdistention of the alveoli and air-sacs of the lung. Two factors play a part in the causation of this condition: first, increase of the pressure under which the air exists in the lung; and, second, degenerative or inflammatory weakness, with loss of elasticity of the lung structure itself. There are several varieties, and the causes vary somewhat in each.

(a) **Acute vesicular emphysema** results simply from excessive air-pressure within the alveoli, and may be more or less widespread. It occurs in cases in which inflammatory swelling or mucous secretions within the bronchi obstruct the expiration of air, but are not sufficient to impede the more vigorous inspiratory force. There results overdistention of the alveoli and air-vesicles. Somewhat similar conditions are present when the entrance of air into certain parts is impeded by obstruction or disease of the bronchi or by consolidations of the pulmonary tissue. Localized emphysema of other parts results (see Fig. 237); the term *vicarious emphysema* is applied to such cases. This is not unusual in the lobules of the lung surrounding areas of pneumonic or tuberculous consolidation, and may affect an entire lobe or lung when the entrance of air into the other lobes or the other lung is prevented (*compensatory emphysema*).

Pathological Anatomy.—In these cases of acute and vicarious emphysema there is simply overdistention of the alveoli, and the tissue presents a paler color than normal and a cotton-like sensation when grasped in the fingers. Microscopically, nothing beyond overstretching of the septa and some anemia of the vessels is apparent. If the causes continue to operate, changes similar to those found in chronic vesicular emphysema ensue.

(b) **Chronic vesicular emphysema** is the ordinary form of emphysema, and is sometimes spoken of as *substantial emphysema*.

Etiology.—Chronic vesicular emphysema commonly occurs in elderly persons, and is predisposed to by attacks of bronchopneumonia and by the existence of other inflammatory and congestive conditions of the lungs. These conditions lead to weakness or loss of elastic tissue in the lungs. Heredity plays a part in the same direction, and it is supposed by some that there is an abnormal lack of development of the elastic tissue in the lungs of such persons, rendering them more susceptible to this disease. The direct exciting cause of emphysema is increase of the air-pressure within the alveoli, and much speculation has been indulged in to discover whether inspiration or expiration plays the more important part in increasing the pressure. It seems likely that the expiratory force is the more important one, as in the case of constant coughing in chronic bronchitis, the blowing of wind-instruments, and the constant straining in certain pelvic disorders, all of which may lead to emphysema. Unusual rigidity of the chest walls, as in abnormal ossification of the costal cartilages, is held responsible for

some cases, the extra force necessary to expand the vesicles being answerable for their dilatation.

Pathological Anatomy.—The lung increases in size, and very often remains distended when the thorax is opened postmortem. The edges are rounded; the organ is light in color, and has a cotton-like feeling when squeezed between the fingers. On section into it the alveoli may be seen to be distended, and there may be cavities of quite considerable size, often as large as a pea, and sometimes even that of a cherry or plum (Fig. 236). Large spaces of this kind are not unusual near the pleural surface; the term *bullous emphysema* has been used in reference to such cases. The pigment matter of the lung is very much lessened, and may be distributed in radiating or parallel lines. This lessening of the pigment is not alone due to its distribution over a greater space, but there is also actual disappearance by removal through the lymphatic channels and through expectoration.

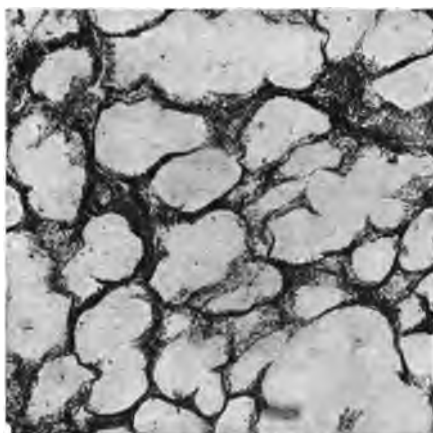


Fig. 236.—Emphysema of the lungs (Karg and Schmorl).

Chronic emphysema may be a general process affecting all parts of both lungs, or it may be localized. In the latter case it is the apex and anterior edges that are most commonly involved, but spots of emphysema may be seen here and there in other parts of the lung, interspersed with normal tissue. The involvement of the apex and anterior portions is due to the fact that the expiratory force is more apt to distend these portions of the lung than the lateral and basal portions, which receive the uniform support of the sides of the chest and the diaphragm as these contract against the lung.

Microscopically, emphysema is found to consist in enlargement of the vesicles and alveoli by distention and by atrophy and disappearance of the intervesicular and interalveolar septa (*atrophic emphysema*). Studied from the earliest stage, there will be found, first, overdistention of the air-sacs, then a gradual thinning, and finally vacuolization of the intervesicular septa at their thinnest parts. Coincidentally, the small

capillaries are compressed, and are finally converted into hyaline cords. The anemia consequent upon this determines additional atrophy and degeneration of the septa and fatty degeneration of the loosened epithelium, so that eventually the whole of the septum disappears. Later, adjacent alveoli intercommunicate and large spaces are thus formed.

The obstruction to the pulmonary circulation due to the obliteration of the capillaries leads to collateral hyperemia of the larger branches supplying the bronchi, and thus prolongs the chronic bronchitis, which in the first instance may have been the cause of the emphysema. Subsequently, collateral anastomosis between the pulmonary arteries and the bronchial system of blood-vessels is established.

Associated Conditions in Other Organs.—The shape of the thorax in emphysema is characteristic. The chest is in a constant state of extreme inspiration, the clavicles elevated, the sternum protruded, the back arched. It has a shape well likened to that of a barrel. The diaphragm is usually depressed and the liver is below its normal position; the heart is almost or completely covered over in front and usually pressed somewhat backward from the chest wall.

Pathological Physiology.—The effect of emphysema upon the circulation is important. The obstruction of the pulmonary capillaries leads to increase of pulmonary pressure, and eventually hypertrophy of the right heart; later, dilatation of the right ventricle ensues, and characteristic cardiac dropsy with general cyanosis may result.

(c) **Senile emphysema** is due to thinning of the intervesicular septa, the result of the atrophic processes to which old age predisposes. There is not necessarily any element of increased air-pressure in the causation of this form of emphysema, and the volume of the lung may not be notably increased, though the tissue is lighter and the air-spaces are found to be increased. The lung is light in color and often collapses readily.

ATELECTASIS

The term "atelectasis" is applied to two distinct conditions, one occurring as a congenital affection, in which the lung has never been properly expanded by air; the other occurring in after life, in which the lung is compressed or collapsed, so that the alveoli and air-vesicles are rendered airless.

Congenital atelectasis is found in newborn babes in whom the inspiratory power has been so deficient, as the result of general weakness or compression of the thorax, or of compression of the brain by cerebral hemorrhage, that the lungs, or parts of them, have never been expanded. It may also take place in a purely mechanical way by obstruction to the air-passages by meconium or other foreign matter.

Pathological Anatomy.—Congenital atelectasis commonly affects the bases and posterior portions of the lung. The area of disease is of a dark reddish color; it is rather tough, and on section presents a smooth appearance; pressure gives no sign of crepitation. If a portion be thrown into water, it sinks. Usually a considerable part of the lung is involved,

but sometimes merely lobular areas are affected. By inserting a blow-pipe into the bronchi the lung may be inflated, and resumes its normal appearance, provided the condition has not persisted for any length of time. If the child does not perish, secondary changes take place. The epithelium of the alveoli degenerates, more or less proliferation of the connective tissues of the septa occurs, and the pleura over the diseased area is prone to become thickened. The atelectatic portion of the lung in such cases remains collapsed; it is smooth on section, free of pigment, and can no longer be inflated. Secondary dilatation of the bronchioles and bronchi may ensue.

It is of interest, in a medicolegal sense, to recognize that atelectasis resembling the congenital form may be met with in the bodies of infants that have lived, breathed, and even cried lustily. The explanation of this is that collapse occurs some time after birth, and, that as the lung has practically still its fetal characteristics, the resulting atelectasis is the exact counterpart of the congenital form.

Atelectasis in later life occurs under a variety of conditions. It may simply be the result of compression of the lung by pleural effusions, by deformities of the chest, by tumors, aneurysms, and the like. It may also be met with in cases in which the bronchial tubes have become obstructed. The larger bronchi may be occluded by the pressure of tumors or aneurysms, or by foreign bodies, and the resulting atelectasis is of considerable extent; the smaller bronchi and bronchioles are frequently obstructed by intense catarrhal thickening of their mucosa, and in consequence lobular areas of atelectasis are developed. The latter is especially frequent as one of the pathological features of bronchopneumonia (*q. v.*).

The explanation of atelectasis as the result of bronchial obstruction has occasioned much discussion, and several theories have been proposed. In some cases it is not unlikely that mucous secretions within the bronchi may prevent inspiratory entrance of air into the lungs without opposing any obstacle to expiration, so that collapse is gradually developed. In other cases it is likely that both inspiration and expiration are prevented, while the air contained within the air-vesicles is gradually absorbed. It is claimed that first the oxygen, later the carbonic acid, and finally the nitrogen are absorbed; the collapse of the alveoli then becomes complete. It is possible, also, that atelectasis may be developed as the result of the failure of respiratory motions on one side, or affecting a certain part of the lung. As a result of this, the elasticity

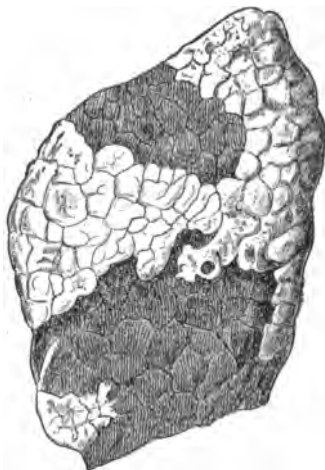


Fig. 237.—Atelectasis due to bronchial obstruction: acute emphysema of the unaffected portions of the lung (Orth).

of the pulmonary tissue would gradually press the air out of the affected area, while new air was not supplied by inspiration. Such a condition, however, must be rare.

Pathological Anatomy.—The part affected by atelectasis is dark in color and is much reduced in size, so that when lobular areas are affected the pleural surface may be considerably depressed (see Fig. 237). On section, the surface is smooth and generally dry, though in some instances passive hyperemia, which is generally present to some extent, reaches such a grade that bloody liquid flows freely from the surface of section. The term *splenization* is properly applied to such cases, whereas the instances in which the surface is dry are often spoken of as *carnification*. The lung does not crepitate, and sinks when placed in water. In the earlier stages the diseased portion may be inflated through the bronchial tubes; but when the condition has persisted, connective tissue overgrowth springing from the septa causes permanent induration and collapse. The lung in such cases is hard and of a dark color, due to the deposit of hematogenous pigment, the result of disintegration of the blood present. The bronchi may be compressed, but sometimes *atelectatic bronchiectasis* results from the increased pressure of air sustained by the bronchi in consequence of the collapsed state of the lung tissue.

INFLAMMATION, OR PNEUMONIA

Classification.—Inflammation of the lungs, pneumonia, or pneumonitis may arise in a variety of ways, and present itself in a number of widely varying forms, both as to the distribution and the nature of the pathological changes in the pulmonary structure. In all cases some irritant is conveyed to the lung either (a) from the upper air-passages or external world through the bronchi (bronchogenic pneumonia); (b) from some other part of the body through the blood (hematogenic pneumonia); or (c) from the pleura by direct extension or through the lymph-channels (pleurogenic pneumonia).

Anatomically, pneumonia is classified according to the nature of the inflammatory products, and there are thus distinguished: *fibrinous pneumonia*, in which the air-vesicles and terminal bronchioles contain an exudate especially rich in fibrin; *catarrhal*, or *bronchopneumonia*, in which the exudate is composed of an albuminous liquid containing numerous epithelial cells and blood-corpuscles; *purulent pneumonia*, in which pus-cells are the noteworthy element in the exudate; *cheesy pneumonia*, in which cellular desquamation and cheesy necrosis are prominent; and *productive* or *fibrous pneumonia*, in which there is overgrowth of fibrous connective tissue. It is to be remembered, however, that mixed cases are of frequent occurrence and that the essentials of inflammation are present in all types. Thus, in many instances localized areas of decided fibrinous pneumonia are found in the midst of larger areas of catarrhal pneumonia; some distinctly purulent exudation may be met with in many instances of fibrinous or catarrhal pneumonia; and more or less productive inflammation and fibrous

overgrowth may be seen in any of the other varieties. Typical cases, however, present little mixture of the lesions.

The terms "parenchymatous" and "interstitial pneumonia" are sometimes employed, but are of doubtful significance. The proper parenchyma of the lungs, the alveolar septa and their contained blood-vessels, are never the sole seat of inflammation, and the term "parenchymatous pneumonia," as usually applied to inflammations of the lining epithelium of the air-vesicles, is, therefore, misused. It is appropriate to call the fibrous variety "interstitial pneumonia."

Fibrinous Pneumonia

Definition.—Fibrinous, or croupous, or lobar pneumonia is an acute infectious form of pneumonia, generally caused by the *Diplococcus pneumoniae*, and usually involving an entire lobe or more than one lobe of one or both lungs. Pathologically, it is characterized by an exudation within the air-vesicles and terminal bronchioles, mainly composed of fibrin; clinically the disease is marked by a definite and characteristic course.

Etiology.—The important factor in the causation of fibrinous pneumonia is the *Diplococcus pneumoniae* (Fränkel-Weichselbaum). This micro-organism is found in the sputa and in the lungs, and is undoubtedly the cause of the pneumonia in the great majority of cases, but some other micro-organisms seem able to occasion typical fibrinous pneumonia. Among these are the pneumobacillus of Friedländer, streptococci, staphylococci, the bacillus of typhoid fever, the bacillus of influenza, and the *Bacillus coli communis*. In some cases in which bacteria other than the diplococcus are supposed to be the cause there is, doubtless, mixed infection; but it must be accepted at the present time that a number of micro-organisms are capable of causing the disease. The fibrinous pneumonia which occurs in the course of tuberculosis is certainly due to secondary infection, and the same thing frequently happens in the course of typhoid fever and influenza, though the specific bacilli of these diseases may alone cause pneumonia.

The micro-organisms usually gain access to the lungs through the bronchi. In the case of the *Diplococcus pneumoniae* the frequent occurrence of this organism in the mouth and upper respiratory passages furnishes a ready explanation of one source of infection. More rarely the bacteria may be directly inspired from without, or, exceptionally, they may reach the lungs through the circulation.

There are certain predisposing factors which have long been recognized clinically as causes of pneumonia. These probably act by rendering the pulmonary tissues less resisting, or by increasing the virulence of the diplococci of the mouth. Among these causes are exposure to cold, injury of the lungs by traumatism, fatigue, and systemic depression.

(For the description of the *Diplococcus*, see p. 280.)

Latest studies have placed this disease, at least when caused by the pneumococcus, among the acute specific infections. There is almost

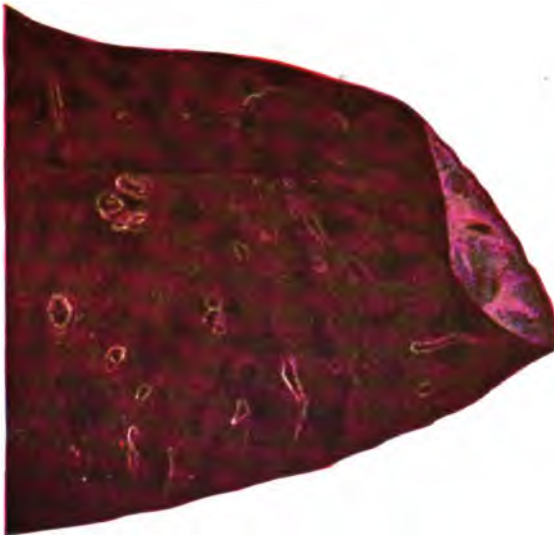
always a bacteremia. While admitting the effect of disposing causes in the production of the disease, attention has been called to acute localized congestions in the lung or bronchioles, as starting-points of the general involvement. Such, says Cole, are the most likely beginnings of the pneumonia because they offer colonizing places for pneumococci. The virulence of the bacterium has little relation to its pathogenicity, but the more virulent, the more fatal. There is no parallel between the severity of the infection and the extent of the anatomical lesions. The leukocytes and their phagocytic power are both increased toward the end of an attack. At its height the infection continues by reason of a state of balance between the phagocytic power of the leukocytes and certain antibodies in the blood on the one hand, and the infectious organisms on the other. When the defensive group neutralizes the offensive, the balance is destroyed and crisis takes place. (See Immunity and *Pneumococcus*, pages 256 and 280.)

Pathological Anatomy.—The lesions most frequently involve the lower lobe of the right lung; next in order is the lower lobe of the left lung; the apices alone are least frequently involved. In all cases there is a tendency to the involvement of a whole lobe, and, as a rule, the entire area of disease is affected uniformly and simultaneously. There are wide variations, however; for, on the one hand, typical fibrinous pneumonia may occasionally appear as a more or less lobular disease (particularly in influenza), and, on the other hand, the process may spread from one part of the lung to another (*pneumonia migrans*). In typical cases not only is the process uniformly distributed, but it passes through distinct stages: first, of congestion, then of consolidation, and finally, of resolution.

Stage of Congestion or Engorgement.—The affected area is dark-red in color; it is swollen and heavy, and on pressure crepitates less than a healthy lung. The pleura over the diseased part is dull and lusterless. On section through the lung, bloody liquid exudes, and when the part is compressed with the fingers this liquid shows a few air-bubbles. The condition is simply one of intense congestion, with exudation into the alveoli and terminal bronchioles of serous liquid and blood-corpuscles (see Fig. 232). Microscopically, the small blood-vessels of the septa are seen to be greatly distended and project inward toward the alveoli. Within the latter may be found many red corpuscles, a lesser number of leukocytes, and some detached epithelial cells.

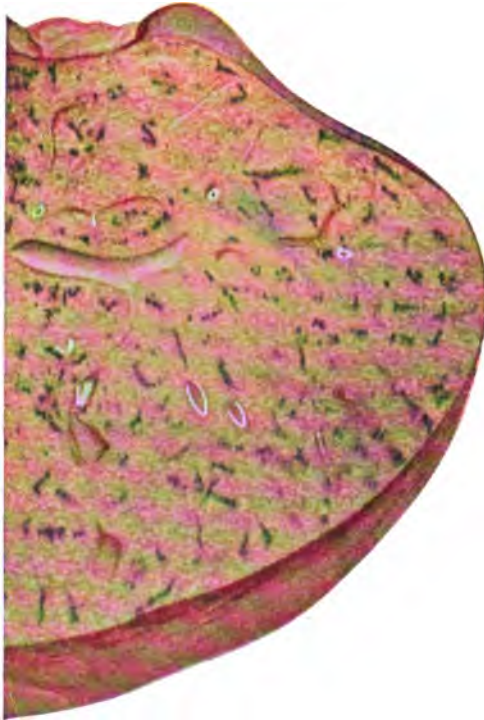
Stage of Consolidation, or Hepatization.—The diseased lung is now completely solid and liver-like in consistency (hepatization). It is swollen, and marked on the surface by indentations of the ribs. The surface of section is at first red in color (red hepatization, Plate 8), but later becomes white or gray, or in elderly persons (in whom the lungs are usually darkly pigmented from inhalation of dust) of a variegated appearance, resembling granite (gray hepatization, Plate 9). The cut surface is entirely dry, and is finely granular on account of the projection of small plugs of fibrin from the alveoli and bronchioles. The pleura is generally covered with fibrinous exudation. Microscopically, the

PLATE 8



Croupous pneumonia, stage of red hepatization (Bollinger).

PLATE 9



Croupous pneumonia, stage of gray hepatization (Bollinger).

alveoli are found distended with a network or particles of fibrin, in which the same cellular constituents as occur in the stage of congestion are embedded. The fibrinous network is beautifully demonstrated by staining the sections after the method of Weigert (Fig. 238). The blood-vessels are less prominent than in the first stage. As the disease advances to the period of gray hepatization the number of leukocytes within the exudate increases and the blood-vessels become still less prominent (Figs. 239 and 240). This change of appearance is due to destruction of red blood-cells and leukocytes, a solution of fibrin by enzymes from leukocytes, and the arrival of new leukocytes, which act as scavengers of the destroyed material. Under the microscope the exudate has retracted from the septa and liquefactive necrosis appears.

Stage of Resolution.—Gradually softening of the exudate occurs and the lung becomes more moist. Puriform liquid may be squeezed from the surface of section, or may be seen in the bronchioles and bronchi. Crepitation is re-established. Microscopically, fatty degeneration of

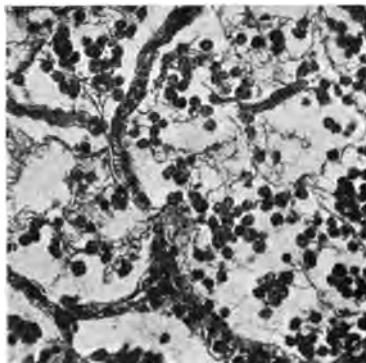


Fig. 238.—Red hepatization of the lung (from a photograph by Dr. Wm. M. Gray).

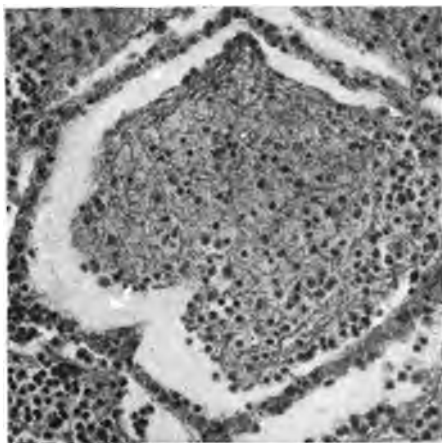


Fig. 239.—Croupous pneumonia: beginning gray hepatization (Karg and Schmorl).

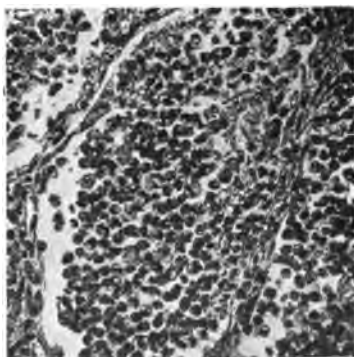


Fig. 240.—Advanced gray hepatization (from a photograph by Dr. Wm. M. Gray).

the cells of the exudate is apparent. Softening is further contributed to by simple liquefaction. The result of these processes is emulsification of the exudate, which is finally carried off by the lymphatics or expectorated.

Resolution occurs by action of the ferments liberated from the infiltrated cells upon their disintegration, and somewhat from the ferments of the bacteria. The digestion products of the ferment action are absorbed, not the cells and fibrin as such.

Before the process of resolution is completed the epithelial cells of the alveoli and bronchioles proliferate, so as to repair the diseased portions. At the same time proliferative changes may be seen in the tissues of the septa. These conditions exist throughout the disease to a slight extent, but become more apparent in the stage of resolution. Eventually the lung is restored to its previous condition.

Unusual Characters.—In some cases the pathological changes vary somewhat from the typical form described. Not rarely there are considerable congestion and even edema of the lung throughout the disease; in drunkards or cachectic individuals the exudate is more markedly hemorrhagic than is usually the case; and sometimes, particularly in instances accompanied by streptococcus infection, the exudate is more cellular than customary. In still other cases proliferative changes in the septa are prominent.

In thinking of the outcome of a pneumonia one must not forget that, in this acute lobar form at least, large parts of the respiratory tissue are functionless, and are deprived of blood-, lymph-, and probably nerve-supply.

Associated Lesions and Pathological Physiology.—The portions of the lung not involved by the pneumonic process are usually somewhat emphysematous and congested, and edema may develop. The latter is, however, not so common as has often been assumed. The larger bronchial tubes, as a rule, remain normal or, at most, become congested. The finer bronchi are more frequently hyperemic, and excess of mucus coats the surface. In practically every case there is a certain degree of fibrinous pleurisy, either on the costal surface of the pleura or between the lobes. Extensive pleurisy is rare and serous exudation is uncommon. The pleurisy is directly attributable to the micro-organism which has caused the underlying pneumonia.

Though fibrinous pneumonia is sometimes a local infection anatomically, systemic intoxication is usually present, and general infection may further aid to develop widespread pathological changes. Leukocytosis is present in the great majority of cases; its absence is generally significant of unusually intense systemic intoxication. In fatal cases white clots are often detected in the chambers of the heart and in the large blood-vessels leaving the heart. Cardiac and respiratory embarrassment, often ascribed to mechanical causes, such as heart-clot or extensive consolidation, is probably in many cases due to the action upon the nervous system of the toxins of the disease. Myocardial degenerations aid in producing circulatory weakness. The heart muscle and the kidneys may suffer parenchymatous degeneration as in other febrile infections, and acute exudative inflammation (myocarditis, nephritis) may occur in either of these organs. Albuminuria is not infrequent, and albumoses may be found in the urine, especially during the stage of

resolution. Calcium, chlorin, and sodium are decreased in excretion, while magnesium and potassium are increased. The spleen is enlarged and soft.

Pericarditis is frequent, and endocarditis, either of the simple or of the malignant type, is more common than in any other acute infection, excepting rheumatism. Meningitis is occasionally noted.

Fibrinous or pseudomembranous bronchitis, laryngitis, gastritis, colitis, and cystitis are sometimes met with. Inflammation of the joints and abscesses in various organs may occur.

Unusual Terminations.—Secondary infection with pyogenic microorganisms may lead to termination in abscess; or this result may be due to the fact that the pneumonia was primarily caused by active pus formers. The affected area may suffer gangrene even more commonly than suppuration. Gangrene is especially prone to occur when

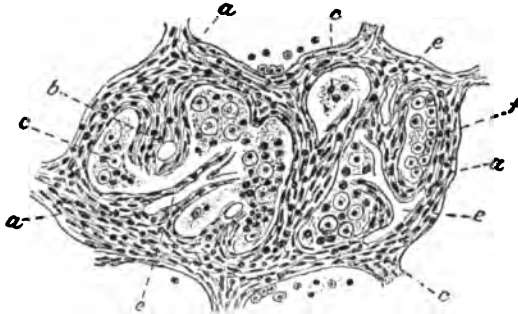


Fig. 241.—Induration of the lung (carnification) in a case of pneumonia of five weeks' duration: *a, a, a*, New connective tissue of the septa; *b*, intra-alveolar proliferation of connective tissue; *c, c, c*, desquamated epithelium in the alveoli; *e, e, e*, new blood-vessels; *f*, lining epithelium of the alveoli (Kaufmann).

the exudation is distinctly hemorrhagic and in cases in which the circulation is specially weak. Finally, resolution may be delayed and productive changes may occur in the septa and even within the alveoli. There results a solidification (carnification) of the lungs, or, as it is termed, *fibrous pneumonia* (Fig. 241).

Catarrhal Bronchopneumonia

Definition.—Catarrhal bronchopneumonia, or lobular pneumonia, is an acute inflammatory affection of the pulmonary tissue, occurring in localized areas and consequent upon inflammation of the terminal bronchioles. Pathologically, the disease is characterized by inflammation of the terminal bronchioles and by exudation into the alveoli of albuminous liquid containing desquamated epithelial cells, together with red blood-corpuscles and leukocytes in varying number; clinically, the disease is marked by an indefinite and irregular course.

Etiology.—Catarrhal pneumonia may be produced experimentally in animals by causing them to inhale steam or various irritating vapors.

Still more characteristic lesions are produced when the vapors inhaled hold decomposing organic matter in suspension. The same result is accomplished by cutting the vagus nerves, as a consequence of which the vocal bands and esophagus are paralyzed and irritating secretions and particles of food are conveyed into the lung by inspiration. In man, tumors, enlargements of the thyroid gland, or inflammatory exudation may compress the vagi and lead to forms of pneumonia similar to the experimental pneumonia of dogs. Somewhat analogously, in the late stages of various diseases, particles of food and mucous secretions may sink to the dependent parts of the lungs, or may be drawn in by the inspiratory air and set up catarrhal pneumonia in the parts already predisposed to inflammation by hypostatic congestion (*hypostatic pneumonia*). Of the same etiological sort are the catarrhal pneumonias which occur in diphtheria, epithelioma of the larynx, and inflammatory conditions of the mouth and pharynx, in which irritating particles are carried to the finer bronchi by inspiration (*aspiration pneumonia*, *deglutition pneumonia*). Catarrhal pneumonia of this kind is not infrequent in the newborn as a result of vigorous inspiratory efforts made while the head is descending through the vagina.

Most frequent, however, of all forms of catarrhal bronchopneumonia is that which occurs in the course of measles, whooping-cough, influenza, or other infectious fevers attended with bronchitis. The manner of involvement of the alveolar structures will presently be described; for the present it may be said that the inflammatory process extends from the bronchi by continuity and contiguity, or by aspiration of irritating bronchial secretions.

The immediate cause of catarrhal pneumonia is some bacterium, the most frequent being the *Diplococcus pneumoniae*, which occurs in over 50 per cent. of all cases, either alone or in combination with the *Streptococcus pyogenes*, staphylococci, the pneumobacillus of Friedländer, the bacillus of influenza or of typhoid fever, or the *Bacillus coli communis*. Any of the other forms named, and especially the pyogenic micrococci, may cause catarrhal pneumonia without the diplococcus of Fränkel; but in the case of fevers (typhoid fever, influenza) in which the specific micro-organisms are found there is usually mixed infection with the *Diplococcus pneumoniae*.

Pathological Anatomy.—The lesions vary somewhat in different cases, and we may distinguish three important types: the simple, or ordinary catarrhal bronchopneumonia, the hypostatic form, and aspiration pneumonia.

1. Simple Catarrhal Bronchopneumonia.—The lung in such cases presents more or less distinct external appearances. On the pleural surface may be seen lobular areas of dark- or light-red or grayish color, which are somewhat elevated and harder than the normal lung. Surrounding these the pulmonary tissue is emphysematous, while here and there may be seen dark-red or lead-colored and somewhat depressed areas of pulmonary collapse (atelectasis). The lung as a whole is crepitant, while the pneumonic and atelectatic areas are consolidated and air-

less and sink in water. On section through the lungs the same general appearances are visible, though the consolidated patches are most abundant near the surface. Both lungs are, as a rule, involved, and any portion is liable to the disease. The smaller and medium-sized bronchi and the bronchioles contain mucopurulent secretion, which may be squeezed out; the areas of pneumonic consolidation are smooth and moist on the surface of section, or exceptionally somewhat granular as a result of admixture of some fibrinous exudate. Occasionally there may be puriform liquid or small purulent collections around the bronchiole in the center of the lobule. The area of collapse (atelectasis) is dark red, as a rule, and on pressure bloody liquid exudes.

In the very earliest stages of the disease the areas of consolidation and collapse may be inflated by inserting a tube into the bronchus supplying the part and by blowing gently into it. Later this is not possible, as the consolidation increases. At the same time it is noted that the

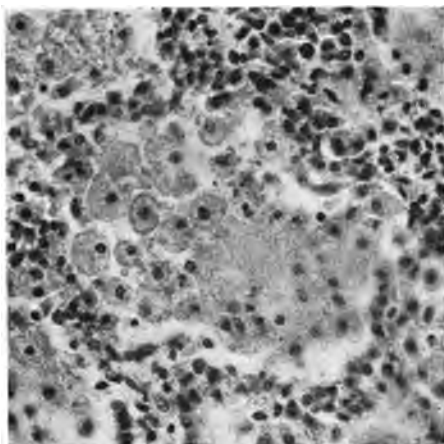


Fig. 242.—Catarrhal pneumonia (Karg and Schmorl).

consolidated areas become lighter in color, until at last they are grayish yellow; while the areas of collapse become pneumonic and present a similar change of color.

Microscopically, the terminal bronchioles and alveolar passages present somewhat swollen walls and contain variable amounts of fluid exudate with many desquamated cells. In the areas of consolidation the alveoli and the air-sacs are filled with liquid and variable numbers of epithelial cells, red corpuscles, and leukocytes (Fig. 242). The epithelial cells are desquamated from the lining membrane either singly or in groups, and there is evidence that active proliferation is taking place as well. In most cases the number of red corpuscles and leukocytes is small, but in some instances, particularly in cases in which streptococci and staphylococci are operative, the exudation may be quite hemorrhagic or, later, purulent. The alveolar septa regularly present considerable round-cell infiltration, and the blood-vessels are sur-

rounded by emigrated leukocytes. The blood-vessels in the septa are distended and tortuous.

The atelectatic areas present even greater congestion of the blood-vessels, and the alveolar cavities are obliterated by the collapse of the walls, or contain, at most, a little hemorrhagic exudate. The epithelial cells tend to lose their characteristic shape and become cuboidal.

As resolution advances, the cellular exudate becomes lighter in color as a result of fatty degeneration, and eventually it is absorbed or expectorated. Coincidentally the round-cell infiltration disappears from the septa, and the pulmonary tissue returns to the normal, excepting that the epithelial cells of the alveoli tend to remain more or less cuboidal for a time. Resolution probably takes place as in the case of fibrinous pneumonia.

Pathogenesis.—The manner of development of the lesions is of considerable interest. In the ordinary catarrhal bronchopneumonia now under discussion there is always a primary bronchitis of the terminal bronchioles, a *bronchiolitis*, or *capillary bronchitis*, as it is termed. This may be spread to the alveolar structure in several ways. In most instances, no doubt, the inflammation travels downward along the bronchioles to their termination by continuity, or outward through their walls to the surrounding alveoli by contiguity. In either case there results a patch of catarrhal pneumonia surrounding a terminal bronchiole. Less commonly the affected lobule first becomes atelectatic and then pneumonic. The atelectasis results from the obstruction of the bronchioles by mucus or by their swollen walls, and is due to the gradual absorption of the air contained within the alveoli and the inability of more to enter (see Atelectasis). Subsequently the collapsed area becomes inflamed by the entrance of micro-organisms from the bronchioles or by extension of surrounding inflammation.

Unusual Characters.—Marked variations are seen in the nature of the process and in its distribution. In some instances there is but little pneumonic consolidation, while the bronchiolitis, or capillary bronchitis, is a striking feature. In other cases the exudate is decidedly hemorrhagic or purulent, and it may in certain areas be quite fibrinous. Regarding the distribution, the most striking variation is the tendency in some cases to lobar involvement by confluence of the lobular areas (*pseudolobar form*).

Associated Lesions.—The constant association of bronchitis has been sufficiently noted. Pleurisy is less common than in fibrinous pneumonia, but the patches near the surface are frequently covered with fresh pleural exudation. It has long been recognized that purulent pleurisy is more apt to occur after pneumonia in children than in adults, and in many of these cases the antecedent pneumonia is catarrhal. Wide-spread toxic and infective lesions may occur, as in fibrinous pneumonia.

Unusual Terminations.—In cases in which micro-organisms, more virulent than usual, cause the pneumonia, suppuration and gangrene may result. Fetid and pultaceous foci, or purulent collections surrounded by considerable areas of congestion and inflammatory edema,

result. In other instances the process of resolution is slow, and fibroid overgrowth of the septa and proliferation of connective tissue within the alveoli ensue, with the production of more or less extensive sclerotic hardening and contraction of the lung structure. Within such areas the alveolar exudate may lie for a long time as a fatty mass; but this is very unusual; and true caseation, of which so much was formerly said, does not occur. The instances in which this was supposed to have occurred were cases of subsequent infection with tubercle bacilli, or cases of tuberculous pneumonia *ab initio*.

2. **Hypostatic Pneumonia.**—The bases and posterior portions of the lungs are commonly involved in these cases. The process occurs as a terminal affection in many diseases. It begins as an intense hypostatic congestion and hemorrhagic edema of the dependent parts of the lungs. Subsequently, the irritants which make their way to the congested area through the bronchi set up a form of inflammation of the terminal bronchioles and air-vesicles which is largely catarrhal, but more fibrinous than ordinary bronchopneumonia. The inflammatory process is also more diffuse, and is at the most insignificant compared with the antecedent and associated congestion and edema.

3. **Aspiration Pneumonia.**—Of the dust which we constantly inhale, the greatest part is arrested in the upper air-passages or in the larger bronchi, and is expectorated. A part, however, reaches the finer bronchi and bronchioles, and sets up a certain amount of local irritation and congestion, with desquamation of epithelial cells and emigration of leukocytes. Ordinarily, these processes are exceedingly trivial and can rarely be demonstrated. In persons, however, whose occupations (*e. g.*, steel-grinding, coal-mining, marble-cutting, etc.) subject them to excessive dust inhalation the pulmonary changes are extensive and severe. This is one form of aspiration bronchopneumonia, but the irritation rarely stops at the point of catarrhal inflammation; on the contrary, the irritant particles penetrate the walls of the bronchioles and are distributed by the lymphatics, causing fibroid changes of greater or less extent. The pneumonia thus produced is, therefore, more appropriately considered as a form of fibrous pneumonia (*q. v.*).

In the course of various affections of the pharynx, larynx, trachea, and bronchi during anesthesia, as well as in cases in which through palsy of the larynx, or through general depression, particles of food or secretions of the mouth enter the air-passages, irritating matters may be inspired or "aspirated" into the finer divisions of the bronchial system. There results intense local irritation, with catarrhal inflammation and consolidation. The exudate is largely epithelial, but more often serous, hemorrhagic, or purulent than in simple catarrhal pneumonia. The condition may be circumscribed to small patches, but if large particles are aspirated and the larger bronchial tubes are obstructed, widespread consolidation, of the character described, results. The inflammatory process in these cases of aspiration pneumonia are habitually intense, and often terminate in suppuration or necrosis, with considerable surrounding hyperemia and edema.

Cheesy or Tuberculous Pneumonia

Definition.—Cheesy or tuberculous pneumonia is an acute or sub-acute form of pneumonia caused by the tubercle bacillus, involving lobular areas or, by confluence of such, an entire lobe or lung. Pathologically, it is characterized by proliferation and desquamation of epithelial cells, infiltration of the alveolar septa, and, finally, by cheesy necrosis in the area of disease. Clinically, the disease presents itself as a more or less acute pneumonic tuberculosis. Caseous pneumonia is frequently associated with miliary or peribronchial tubercles, affecting the alveoli adjacent to the tubercles.

The pneumonic form of phthisis florida is a caseous pneumonia. Bronchopneumonia of coccus origin may supervene upon chronic ulcerative phthisis, or tuberculous lesions may be implanted upon a pneumonia.

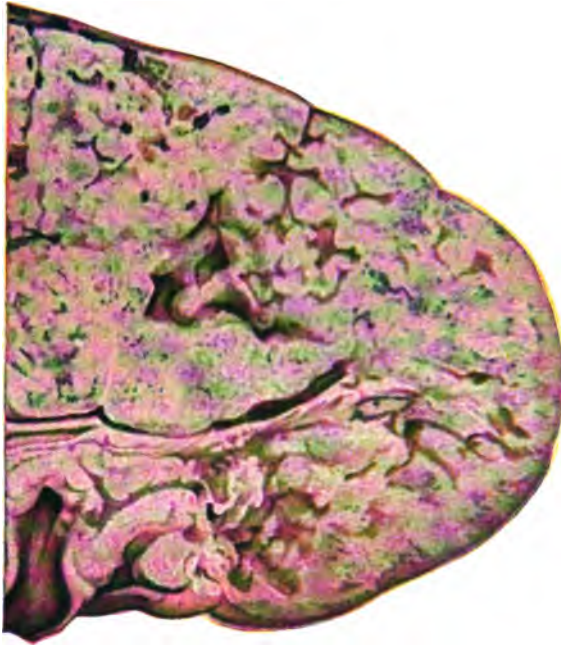
Etiology.—Cheesy pneumonia as an independent condition is more common in children than in adults. The immediate cause is the tubercle bacillus. Infection occurs by rupture of a tuberculous gland or cavity into one of the bronchi and dissemination of the infective material throughout the lung. Likewise, bacilli may be inhaled from outside, or from tuberculous foci in the bronchi, larynx, or nose. In cases of disseminated tuberculosis of the lungs areas of caseous pneumonia are habitually encountered in the pulmonary structure between the tubercles. Finally, infection may take place through the blood, but the occurrence of caseous pneumonia rather than miliary tuberculosis in such cases is assuredly rare. Theoretically, it is possible to have a sudden and overwhelming generalization of the tubercle bacillus with involvement of a *whole* lung, but such an occurrence is rare. Such cases have been described, but it is difficult to estimate the importance of the tubercle bacillus in the presence of other germs capable of producing the inflammation. The process is a catarrhal *pneumonitis universalis* without the tubercular changes characteristic of caseous pneumonia.

It has, indeed, been questioned whether the tubercle bacillus alone can cause this caseous pneumonia, since the typical tuberculous inflammation is a productive one of lymphatic or interstitial origin. On the other hand, a caseous pneumonitis without tubercle bacilli is not known. In those cases reported as *primary* diffuse tuberculous pneumonia the pre-existence of a focus discharging bacilli into the trachea or bronchi could not be satisfactorily excluded.

Mixed infection with *Diplococcus pneumoniae* is not infrequent, but it is not, as some investigators have maintained, essential to the disease.

Pathological Anatomy.—In its most typical form caseous pneumonia is a lobular process beginning around the terminal ends of the bronchioles, where the infective material lodges. The lung presents on section areas of consolidation not unlike those seen in catarrhal bronchopneumonia. At first these are congested and red in color, but very soon degenerative changes cause a grayish or yellowish color. The surface of section is usually smooth, but often somewhat granular from asso-

PLATE 10



Subacute caseous (tuberculous) pneumonia (Bollinger).

ciated fibrinous exudation. When abundant infection has occurred the areas may be thickly set, and a lobar form is thus established (Plate 10); or there may be a gradual involvement of new areas, receiving their infection from those first formed, causing a similar, but less uniform, lobar pneumonia.

The distribution of caseous bronchopneumonia depends upon its origin. If this be from the upper air-passages, the involvement may be more or less regular and symmetrical, while if entrance of the bacilli be gained through a rupture of a gland into a bronchus, it will follow the course of this tube and spread from it.

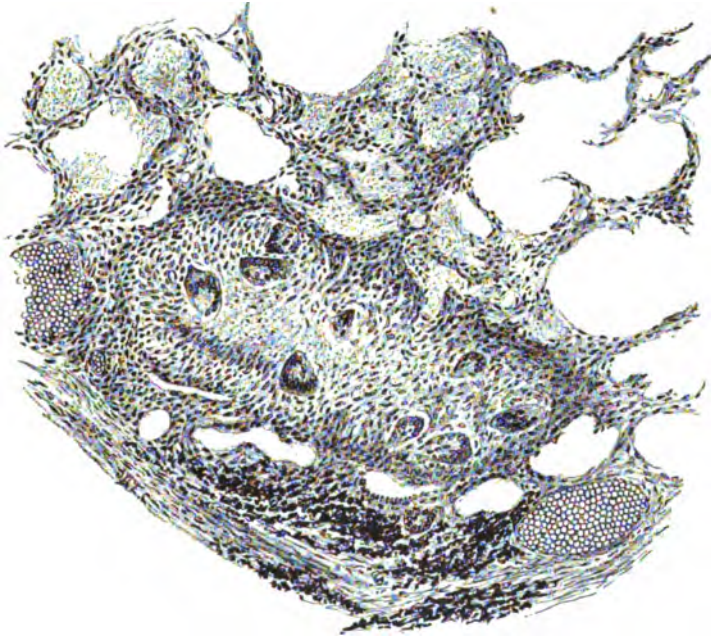


Fig. 243.—Peribronchial tubercle of the lung and caseous pneumonia of the adjacent alveoli.

Caseous pneumonia shows no tendency to resolution, but, on the contrary, tends to progressive cheesy degeneration, and at last to the formation of cavities. The entire lung may be riddled with small excavations, presenting ragged, cheesy walls. Usually the cavities are small, even though there be few; exceptionally, large ones are seen. Though resolution does not occur, limited areas may be healed by reactive fibrous overgrowth springing from the alveolar septa and encapsulating the diseased area, or penetrating it, and transforming the whole into a fibrous mass.

Microscopically, the exudation has many of the characters seen in catarrhal bronchopneumonia. Essentially, the exudate is cellular, and is principally composed of large epithelial cells. These are the desquamated and proliferated lining cells of the alveoli. A smaller number

of red blood-corpuscles and leukocytes is noted, but they are unessential. Sometimes a fibrinous network may be seen in the alveoli, but quite as often this is wholly wanting. The blood-vessels are engorged at first, and the septa are infiltrated with round and spindle cells. The walls of the blood-vessels themselves may be thickened by proliferation of the connective tissue. As the process advances the cellular exudate and the alveolar walls as well undergo cheesy degeneration, and present a granular appearance under the microscope (Fig. 243).

Associated Lesions.—Cases of typical caseous pneumonia, as above described, are rare; as a rule, more specific tubercular lesions (tubercles) are associated. The smaller bronchi are commonly attacked in association with caseous pneumonia, and tuberculous bronchitis and peribronchitis tending to cheesy change result. The pleura may be covered with inflammatory exudation, or may present miliary tubercles over the area of disease. Associated pleural involvement is especially common between the lobes. The lymphatic glands of the anterior mediastinum and around the bronchi are frequently enlarged, and may be cheesy in the later stages.

Fibrous Pneumonia

Definition.—Fibrous, or productive, pneumonia is a chronic process resulting from continued irritation, and involving small or large areas of the pulmonary structure. Pathologically, it is characterized by overgrowth of connective tissue, and clinically it is marked by signs of more or less extensive mechanical impairment of the pulmonary functions.

Classification.—Several quite distinct forms, depending upon different modes of causation, may be described. The principal varieties are: (1) The pneumonokonioses, or fibrous pneumonias, due to dust inhalation; (2) the secondary indurative pneumonias, such as sometimes follow croupous, catarrhal, or caseous pneumonia, or more frequently chronic congestion of the lungs or atelectasis; (3) pleurogenetic fibrous pneumonia, in which the process arises by extension of chronic pleural disease; and (4) peribronchial and perivascular fibrous pneumonia, in which the process follows the bronchi and pulmonary arteries.

1. **Pneumonokoniosis.**—Of the dust we constantly inhale, but a small part reaches the finer divisions of the bronchial tree. Most of it adheres to the walls of the upper respiratory tract and is discharged with the sputa, either free or enclosed in leukocytes or epithelial cells (*dust-cells*, *Staubzellen*). When fine particles reach the terminal bronchioles they occasion catarrhal inflammation, marked by proliferation of the epithelium and exudation of leukocytes. These cells may envelop the irritant particles and remove them through the expectoration. When, however, the dust has sharp edges (as in coal-dust, iron-dust, marble-dust, etc.), and especially when the quantity inhaled is considerable, removal by expectoration becomes more difficult. In such cases the foreign particles penetrate the walls of the bronchioles and alveoli, passing between the epithelial cells. They may be arrested in the

alveolar septa and in the tissue surrounding the bronchioles by the formation of a zone of inflammatory exudation, which eventually organizes, forming a fibrous capsule. Some of the particles, however, move along the lymph-spaces into the lymphatic vessels, being carried by phagocytes or floating free in the liquid. These particles may be arrested at various points along the lymphatics, and may occasion fibrous thickening of the vessels or of the perilymphatic tissue. The greater portion, however, passes to the lymphatic glands at the root of the lung and surrounding the bronchi, and indurative enlargement of these structures results. In exceptional instances the irritant particles may be conveyed still further, being deposited in the glands about the smaller curvature of the stomach and beneath the fissure of the liver. This unusual distribution in a direction opposite the usual lymphatic current is explained by the assumption that obstruction of the larger pulmonary lymphatics causes a reversal of the current. Metastatic distribution of dust-particles may also be due to rupture of one of the affected lymphatic glands into a vein. (See discussion of Pneumonokoniosis, page 99.)

Pathological Anatomy.—The appearance of the lung varies with the amount of dust inhaled and with its nature. In cases of moderate degree small areas of fibrous thickening, with puckering, are the only abnormality. On section, these are found to be hard and of grayish color; often, however, darkly pigmented, owing to the character of the particles inhaled as well as on account of the formation of hemorrhagic pigmentation. The fibrous tissue may be arranged in a stellate fashion, or concentrically around a nucleus of foreign matter. Secondary changes are not uncommon; calcification is frequently observed, and true bone-formation is occasionally noted. Such areas of localized pneumokoniosis are very commonly met with near the apices.

More extensive induration is rare, and is rather more frequent at the bases. Large areas of induration may completely destroy the vesicular character of the lung structure. Firm bands of connective tissue may follow the bronchi and radiate into the peripheral portions of the lung, or thickened trabeculæ may pass from the pleural surface toward the interior, or, again, a more uniform sclerosis may exist throughout the organ. The organ is contracted; the pleura, as a rule, is thickened and drawn inward; and the bronchi may be widely dilated as a result of the traction of the contracting connective tissue and as a consequence of accumulating secretions within. Extensive adhesions to the chest wall often cause deformities of the chest, and the pericardium, heart, and other mediastinal structures may be drawn from their normal positions.

In rare cases the epithelium of the alveoli and finer bronchioles proliferates, and later undergoes a certain amount of fatty degeneration, giving rise to an appearance not unlike caseation. In still other cases necrosis, suppuration, and cavities (non-tuberculous) are observed.

Microscopically.—In the beginning stages round-cell infiltration and connective-tissue proliferation may be seen around the foreign particles in the septa, and a certain amount of catarrhal inflammation

may be present in the alveoli. Sharp-edged particles often occasion small hemorrhages. In the later stages dense sclerotic tissue characterizes the process. Proliferative inflammation of the epithelium of the alveoli may be present, but more often the cells undergo atrophy and disappear.

Varieties.—Certain varieties, dependent upon the kind of dust inhaled, have been described. The term *anthracosis* is applied to those instances in which coal-dust is the irritant. To a moderate extent this is seen at every autopsy in persons of adult age, but the cases in which conspicuous sclerosis has occurred from this cause are met with only in coal-miners and persons of similar occupations. The lung is of a marble-like or slate-like appearance, and the lymphatic glands around the bronchi are intensely pigmented. *Siderosis* is the designation of the cases of pneumonokoniosis due to iron-dust, as seen in grinders, founders,

etc. *Chalicosis* is the term applied to the form due to stone-dust, as seen in potters, marble-cutters, etc.

The variety of pigment may be distinguished by microchemical reactions.

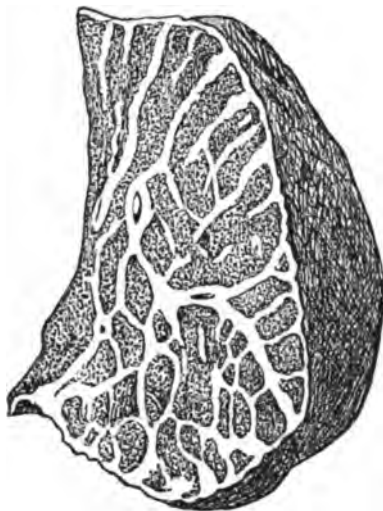


Fig. 244.—Fibrous pneumonia secondary to chronic pleurisy (Kaufmann).

2. **Secondary fibrous pneumonia** sometimes occurs after croupous or catarrhal pneumonia, or atelectasis, and in these cases appears in the form of uniform or localized induration of the pulmonary structure. It is due to reactive inflammation of the septa, causing thickening of the latter, as well as proliferation within the alveolar exudate. Similar reactive fibrous change is seen in some cases of caseous pneumonia, and in chronic phthisis the cavities are quite generally walled by fibrous tissue.

Finally, chronic congestion of the

lung, such as occurs in valvular diseases of the heart, particularly mitral disease, frequently leads to diffuse sclerosis of the lung. Such cases are distinguished by dilatation of the veins and by hematogenous pigmentation.

3. **Pleurogenic fibrous pneumonia** is an occasional consequence of chronic pleurisy. The lung presents on section dense trabeculae of fibrous tissue, which extend from the thickened and sclerotic pleura deep into the pulmonary structure (Fig. 244).

4. **Peribronchial and perivascular fibrous pneumonia** may be associated with the pleurogenic form, or the overgrowth of connective tissue around the bronchi and vessels may start at the root of the lung and extend toward the periphery. The latter form has been described by some observers as especially liable to result from syphilis. More moder-

ate peribronchial and perivascular fibrous pneumonia occurs in association with other forms, as the pneumonokonioses and secondary fibrous pneumonias, but in these cases it is but a minor part of the process.

Congenital Syphilitic Pneumonia.—A form of *productive pneumonia*, as distinguished from fibrous pneumonia in the strict sense that the latter is characterized by formation of sclerotic fibrous tissue, is met with in congenital syphilis. This is the *pneumonia alba* of some writers. *Spirochæta pallidæ* are present in countless numbers. It is characterized by great proliferation of round and irregular connective-tissue cells, with more or less multiplication and degeneration of epithelial cells in the alveoli and bronchioles. The lung is solid, airless, and white in color (*white pneumonia*). Gummata may be associated.

Purulent Pneumonia

Definition.—Purulent pneumonia is an acute form of pneumonia in which the exudate undergoes purulent softening, usually caused by the pus producing cocci. Pathologically, it is characterized by purulent and hemorrhagic exudation in the connective tissue, lymphatic channels, or terminal bronchioles and alveoli; and clinically it is marked by evidences of intense septic infection as well as by great pulmonary embarrassment. This subject is given a separate heading by reason of its clinical rather than pathological importance, as the dominant factor is septicemia.

The infection in purulent pneumonia may reach the lungs through the bronchi (bronchogenic), the blood-vessels (hematogenic), or the subpleural lymphatics (pleurogenic or lymphogenic).

Bronchogenic purulent pneumonia has already been referred to in the description of fibrinous pneumonia and catarrhal bronchopneumonia. It is particularly frequent in the latter, in some cases of which considerable purulent exudation may be seen in the alveoli or, in the form of small purulent collections, in the intervesicular septa. The pathological changes are those of catarrhal pneumonia, with an excessive infiltrate of polynuclear leukocytes. These are instances of intense infection, and the majority of such cases are due to the *Streptococcus pyogenes* or to staphylococci. The pneumococcus may, however, be found alone. The most decided purulent bronchopneumonia is seen in instances of aspiration pneumonia secondary to a suppurative process in the upper respiratory passages, in which particles of infective material are inspired and lodge in the bronchioles.

Purulent pneumonia is rarely met in the course of fibrinous pneumonia, but sometimes occurs as a terminal condition. Abscesses of considerable size may be formed.

Hematogenic purulent pneumonia is secondary to suppurative or gangrenous processes in other parts of the body, and is a manifestation of pyemic infection. It is frequent in puerperal septicemia, in suppurative osteomyelitis, and like conditions. The micro-organisms are

carried by the veins to the right heart, and may first set up malignant endocarditis, from which embolism takes place, or they may pass directly through the right heart to the lungs. As a rule, the micro-organisms in question are either streptococci or staphylococci; but in certain specific infections (as typhoid fever) the specific organisms may alone occasion purulent pneumonia.

When large embolic masses reach the lungs occlusion of larger branches of the pulmonary artery occurs and hemorrhagic infarcts are formed. In the earliest stages these appear as more or less well-circumscribed areas of hemorrhagic infiltration of dark-red color. Very soon change of color occurs, and the foci alter to a grayish, then a yellowish, color, and finally liquefy, forming suppurative cavities, with irregular walls. The lesion at this stage constitutes what clinicians describe as *abscess of the lung*, and though such abscesses may result from fibrinous pneumonia or other conditions, the most frequent variety is that following embolism or thrombosis of the pulmonary artery. The tissue around the abscess is intensely engorged and edematous, and not rarely quite hemorrhagic. Microscopically, the lesion in the earlier stages presents the appearances of a catarrhal and hemorrhagic pneumonia. The abscesses frequently break into the bronchi and discharge their contents; more rarely rupture into the pleural sacs occurs. The pleura itself is intensely inflamed over the embolic areas, and, as a rule, is covered with fibrinopurulent exudate. Extensive purulent pleurisy (*empyema*) may occur.

When the micro-organisms reach the lung in a more disseminated manner they pass at once to the smaller arterioles and capillaries. The organisms circulating in the blood are, in all probability, single, but when they meet the intricacies of the pulmonary capillary network they are arrested. The oxygen present favors agglutination of bacteria, especially of the pneumococci. The swelling of the vascular endothelium by toxic agencies, in all general infections, favors the settling of bacteria.

Embolic infarcts are wanting in such cases, but there is diffuse serous, hemorrhagic, catarrhal, and purulent exudation, which causes consolidation of a somewhat gelatinous character. Small foci of suppuration (miliary abscess) may be seen, and the purulent process may visibly extend to neighboring parts of the lung along the lymphatic vessels.

Terminations.—In either of the above forms, the localized embolic or the diffuse, necrosis or gangrene of the pulmonary tissue may occur. Occasionally recovery takes place by absorption of the purulent exudate or by its discharge. As a rule, the disease is fatal.

Pleurogenic purulent pneumonia follows intense pleurisy, usually of purulent type. Infection of the subpleural lymphatics first ensues, and later the purulent process extends into the lung within and around these vessels (*purulent lymphangitis* and *perilymphangitis*), in the form of yellowish streaks or bands, which surround the veins and bronchi and follow the interlobular fibrous tissue in various directions. The lobules of the lung may be so pushed apart that the term *pneumonia*

desiccans is quite applicable. The proper substance of the lung adjoining the paths of purulent invasion, and under the pleura, frequently shows the same form of hemorrhagic and purulent pneumonia as occurs in the diffuse hematogenic form.

Associated Lesions.—Widespread pyemic and toxic lesions are often found in association with purulent pneumonia, but they are often merely coincident results of the same primary disease to which the pneumonia owed its origin, rather than the consequences of the purulent pneumonia itself. Secondary infections may, however, occur, such as malignant endocarditis of the left side of the heart, septic nephritis, and the like.

GANGRENE

Gangrene of the lung results from the action of putrefactive micro-organisms in necrotic areas of the lung tissue. It may be the consequence of direct extension of carious conditions of the ribs or other adjacent bony structures through the pleura into the lung, or of the extension of necrotic processes from ulcers or cancerous disease of the esophagus or stomach. In other cases the infective materials reach the lung through the inspired air, coming from ulcerative processes in the upper air-passages or from without. When foreign bodies lodge in the bronchi, or the latter are obstructed by the pressure of tumors or aneurysms, there may be, first, more or less congestion and pneumonic consolidation, followed by secondary infection and gangrene. In still other instances the infective material reaches the lung through the blood. Finally, gangrene is sometimes a terminal process in pneumonia, tuberculosis, and hemorrhagic infarction of the lungs. Certain general conditions predispose more or less to it. Thus, in diabetic individuals, congestions or pneumonia are prone to terminate in this way, and engorgement of the veins or passive hyperemia always renders the lung more liable.

Pathological Anatomy.—Gangrene may appear as a circumscribed or diffuse process. In circumscribed gangrene more or less extensive areas of lung present a dark, reddish, brownish, or even greenish appearance, and are surrounded by a zone of intense congestion or of pneumonic consolidation, often of purulent or hemorrhagic type. The diseased part is soft, pultaceous, and foul in odor. Later it may break down into a putrid mass, and may discharge through the bronchial tubes, severe pulmonary hemorrhages sometimes occurring at the same time. The bronchi and the blood-vessels often escape the process, and may pass through the gangrenous area without being themselves materially affected; but usually the bronchi are penetrated, and the blood-vessels, after they become occluded by thrombosis, suffer the fate of the other tissues. The process may extend widely from a single focus, or reactive inflammation may establish a fibrous capsule, and after discharge of the gangrenous material through the bronchi, healing by the formation of a scar may terminate the disease.

Diffuse gangrene does not differ much in its general appearances,

but is less intense and, in general, more widespread. The affected area is of a dark-red or greenish-black color, soft and edematous, or sometimes dry, and has a somewhat fetid odor, as in the circumscribed form. Spots of hemorrhagic infiltration and of softening, with formation of cavities, may be noted.

The sputa in gangrene are mucopurulent, of a yellowish-gray or brownish color, and intensely fetid. When placed in a conical vessel they separate into three layers: the upper frothy, the lower puriform and brownish in color, and the middle layer more fluid and yellowish.

INFECTIOUS DISEASES

Tuberculosis

Tuberculosis of the lungs is usually a local process at first, but in many cases becomes generalized by subsequent spread of the infection. Sometimes the pulmonary disease is from the beginning only a part of a general tuberculosis.

Infection of the lungs occurs through the bronchial tubes (*bronchogenic tuberculosis*), through the blood-vessels (*hematogenic tuberculosis*), or through the lymphatic system (*lymphogenic tuberculosis*).

1. The first of these three modes of infection is probably far more frequent than the other two combined. The tubercle bacillus, disseminated by the drying of sputa or other infected discharges from tuberculous patients, is carried directly to the lungs in the inspired air or, more rarely, it may lodge in the pharynx, upper air-passages, or bronchi, and produce primary tuberculous lesions from which the lungs are secondarily affected. Immediate infection of the lungs is more frequent than the secondary form.

2. Hematogenic infection is clearly evident in cases in which a tuberculous disease of some other part (as the bronchial glands, prostate, bones, etc.) has become generalized by entrance of the tubercle bacilli into the circulation and in which tuberculous lesions make their appearance in various parts of the body, including the lungs. Sometimes the point of rupture of a tuberculous focus into a vein has been demonstrated. The bacilli entering the venous circulation are carried through the right heart to the lungs, and are, for the most part, arrested in them. When finely divided in the blood some may pass through the pulmonary circulation and may thus be distributed widely through the body. In many cases, however, the lungs arrest all the bacilli and become affected without general tuberculosis. Sometimes perhaps the lungs are infected through the vascular channels without pre-existing lesions elsewhere. This may occur when tubercle bacilli traverse the mucous membranes and enter the circulation without causing a primary lesion at the portal of entrance. How frequently this may happen cannot very well be estimated, but many facts speak in favor of its not infrequent occurrence. Tuberculosis of the mesenteric glands without intestinal lesions is not uncommon, and cannot be explained

except on the assumption that the bacilli passed through the mucosa and into the lymphatics without causing a lesion at the portal of entrance. Other facts (as, for example, the occurrence of primary tuberculosis of bones) indicate that the bacilli may be distributed widely in the circulation without local lesions at the places where they entered the body. Lung tuberculosis can doubtless occur in the same way, and some authorities believe this a frequent mode of infection. In view of the demonstrated intercommunicability of human and bovine tuberculosis, the possibility of pulmonary infection from the consumption of tuberculous meat and milk and the passage of the bacilli through the mucosa of the digestive tract is apparent.

In some cases of hematogenic tuberculosis the bacilli gain entrance to the blood in an indirect manner, as, for example, when a lesion of the abdominal or thoracic lymph-glands penetrates the thoracic duct. The bacilli carried in the lymphatic stream pass through the thoracic duct and eventually reach the blood and are disseminated in the lungs and other organs.

Localized hematogenic tuberculosis of the lungs may occur when an old tuberculous lesion of the lung or a caseous bronchial lymph-gland penetrates a branch of the pulmonary artery and thus disseminates bacilli in the lungs. This mode of occurrence of the disease in the lung is rarely observed.

3. Lymphogenic infection of the lungs is secondary to tuberculous pleurisy, tuberculous bronchial lymphadenitis, mediastinitis, etc. In these cases the pleural and subpleural lymphatics become infected and the process spreads along these channels to the lungs.

A combination of the aërogenic and lymphogenic routes is possible. It is believed that tubercle bacilli may settle on the mucosa of the upper air- and alimentary passages, be carried thence to the regional lymph-nodes, and finally to the mediastinal or bronchial glands, where they may involve the lung by extension or rupture. Still, again, the lymphatic channels may combine with the alimentary tract, and, as has been discussed under Anthracosis and the Tubercle Bacillus, the organisms may reach the root of the lung by the lymphatic chain along the posterior midline of the body. This and the direct bronchogenic invasion form the principal infection tracts for Koch's bacillus.

Bronchogenic Tuberculosis

Larger masses of infective material inhaled in respiration may lodge in the bronchi or larger bronchioles and set up tuberculous ulcerations, from which smaller particles may be secondarily aspirated into the finer divisions of the bronchial tree. Such an occurrence, however, is extremely rare. More commonly the tubercle bacilli are inhaled in a state of extreme dissemination, and are not arrested until they reach the point of division of the terminal bronchioles into the alveolar passages. One of two results may occur at this point: either there is set up a limited area of caseous or tuberculous pneumonia,

or the bacillus penetrates between the epithelial cells without producing a definite intra-alveolar lesion and causes specific tuberculous changes in the peri-alveolar and peribronchial connective tissues (miliary tubercles). It has been the occasion of some dispute among pathologists to decide which of these processes is most apt to arise when the infection occurs through the bronchial tubes. Undoubtedly, both kinds of change may take place, and it seems likely that in most instances there is a mixture of the two forms. When the infective material is in great abundance and is particularly virulent, and in cases in which the individual is especially vulnerable, caseous pneumonia predominates over the formation of tuberculous nodules. On the other hand, a less abundant infection or greater resisting power on the part of the individual determines a greater liability to the formation of nodules and less likelihood of extensive caseous pneumonia. Whichever lesion, however, is primary, the other soon becomes associated. Thus, if the epithelia of the alveoli are first affected with production of caseous pneumonia, the peri-alveolar connective tissues are soon involved, and tubercles form *in loco*, or, by dissemination of the bacilli along the lymphatic channels of the peri-alveolar connective tissues, tubercles appear at some distance from the first lesion. The alveoli contiguous to such secondary tubercles may in the next place become involved in caseous pneumonia. When the primary lesion is a tubercle in the peri-alveolar connective tissue, the adjacent alveoli in the same manner suffer caseous pneumonia. Thus, the disease spreads through neighboring lobules and in time affects considerable areas of the lung.

Degenerative changes soon make their appearance. The areas of pneumonia, which began as small foci or as larger areas of lobular tuberculous pneumonia, change their color from a grayish to a yellowish color and become completely caseated; while the secondary tubercles in the neighborhood, or those which were primarily formed, similarly become opaque and lusterless, and finally yellowish by caseation. The blood-vessels in caseous pneumonia or in the tubercles are inadequate to supply sufficient nourishment to the tissue. In the pneumonic areas this is due to proliferative changes in the intima and to direct pressure of the exudate, while in the tubercles it is due to hyaline and other forms of degeneration, with collapse of the walls.

Coincidentally with the process just described, round-cell infiltration and proliferative changes are manifest in the structures surrounding the diseased areas. In the case of the areas of caseous pneumonia, infiltration and proliferation of the connective tissue of the septa, as well as proliferative changes in the blood-vessels of these parts, are observed. There is a wide variation in particular instances in the degree of these reparative processes, and in general it may be said that the more acute the disease, the more apt is degenerative caseation to take place and the less likely regeneration to occur. Similar overgrowth and infiltration may be seen around the tubercles, and in favorable instances the latter may eventually be completely encapsulated or converted into a fibrous nodule. In instances in which the reparative processes are very exten-

sive there may eventually be a preponderance of connective tissue over caseous pneumonia or miliary tubercles.

Varieties.—We may distinguish all of the forms of bronchogenic tuberculosis by the name of *pneumonic tuberculosis*, from the fact that the element of caseous pneumonia is always an important one, and separates them sharply from hemogenic and lymphogenic tuberculosis, in both of which the formation of miliary tubercles predominates over other processes. It must, however, be remembered that in some cases of hemogenic tuberculosis the lesion may take the form of a localized pneumonic tuberculosis by reason of the fact that the first-formed miliary tubercles are soon obscured by a more extensive pneumonic process.

Three forms of pneumonic tuberculosis are met with: the acute, which is frequently spoken of as *acute caseous phthisis*, or *galloping consumption*; the chronic, which is also known as *chronic ulcerative phthisis*; and the form in which fibrous overgrowth predominates, and which is, therefore, known as *fibrous* or *fibroid phthisis*. While typical instances of these forms are quite distinct, there is no sharp dividing line separating the groups, and individual forms merge insensibly one into the other.

Acute pneumonic tuberculosis is more common in children than in adults. Two elements play a part in its occurrence: first, a high degree of susceptibility; and, second, abundant infection with virulent bacilli. The latter may be derived from without the body by direct inhalation, or may come from the discharge of older caseous areas in the lungs which have broken into the bronchial tubes, or from some focus of tuberculosis in the upper air-passages.

Pathological Anatomy.—This form of tuberculosis is lobular, but very frequently by confluence of the affected areas an entire lobe may be involved. Either the base or the apex may be first affected. On section the lung presents a more or less variegated appearance in the earlier stages, due to the formation of minute patches and lobular areas of caseous pneumonia having a grayish appearance, and the coincident congestion of surrounding portions of the lung tissue. Sections through the lung which cut a terminal bronchiole in a longitudinal direction show it more or less filled with cheesy exudate and surrounded by peribronchial caseation (Fig. 245). Transverse sections give the appearance of a section through a large tubercle or an aggregation of tubercles, but the lumen of the bronchiole may usually be discovered in the center or to one or the other side. Small miliary tubercles may be apparent in the edges of the pneumonic patches, and even for some distance around them, but the connective tissue involvement is more apt to appear as a diffuse infiltration along the peribronchial and perivascular lymphatics than as distinct tubercles. As the process increases the lung tissue becomes more and more extensively involved and uniformly gray or yellowish and consolidated (Fig. 246). The cut section is generally somewhat granular in the earlier stages from admixture of fibrinous exudation in the alveoli; but later progressively increasing caseation and softening render the surface of section smooth and moist. Not infre-

quently complete destruction takes place and cavities are formed. These are usually small and present no marked tendency to the formation of an organized wall, but appear simply as necrotic excavations with irregular, ragged outlines. The pleura over the surface of such a lung is usually inflamed and covered with more or less fibrinous or fibrinopurulent exudation, and not rarely with an abundant crop of tubercles. Sometimes a superficial lesion may rupture into the pleural cavity and cause pneumothorax or, later, pyopneumothorax.

When the process is less active and the infection less abundant, confluence of the lobular areas is less likely to occur, and there are seen merely disseminated patches of caseous pneumonia scattered through various parts of the lung, which is, in general, more or less congested. In such instances, too, the evidences of reparative change are more decided. Complete encapsulation with subsequent calcification may ensue, or fibrous overgrowth may convert



Fig. 246.—Extensive bronchogenic tuberculosis (caseous pneumonia) of the base of the lung (Orth).

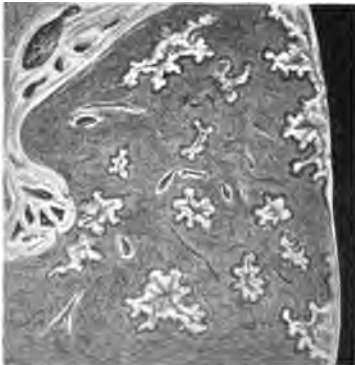


Fig. 245.—Bronchogenic tuberculosis of the lung, showing the involvement of the tissues surrounding the terminal bronchioles (Birch-Hirschfeld).

the entire area into a cicatricial mass. If the cheesy area is simply enclosed with fibrous tissue, it may remain quiescent for a time, possibly for years, and subsequently penetrate the enclosing wall and occasion a fresh extension of the whole process.

Chronic pneumonic tuberculosis is the ordinary form of pulmonary phthisis. It begins in the apices of the lungs in the great majority of cases, though children are as likely to be first affected at the bases as at the apices. The apices present areas of low resistance because of their short excursion of motion and the slow gaseous interchange. They are slightly less vascular than lower lung portions.

While there is no doubt that chronic phthisis is usually due to infection through the inspired air, it must be admitted that occasionally the onset of the process is due to infection through the blood or lymphatic channels (see p. 566). In the instances of the latter kind there may first be established a localized lesion which caseates and penetrates a bronchial tube, discharging its contents, and thus leading to widespread bronchogenic infection. The further development of the disease takes place in several distinct ways (see below).

Pathological Anatomy. — When there has been a pre-existing bronchitis, adhesion of the bacilli may occasion tuberculous bronchitis with ulceration and secondary involvement of the surrounding tissues. More commonly the bacilli lodge in the finer bronchioles or alveolar passages, as in acute pneumonic phthisis, and give rise to lobular areas of caseous pneumonia, surrounded by tubercles which are formed along the course of the lymphatic vessels leading out from the first-formed caseous foci. There is a tendency to a constant increase of the area of disease by the discharge of caseous material into



Fig. 247.—Tuberculous cavity of apex of lung communicating with bronchus, as shown by rod (from a specimen in the collection of Dr. Allen J. Smith).

contiguous bronchi and its aspiration into other parts of the lung, and also by dissemination of the infection along the lymphatic vessels traversing the connective tissue around the blood-vessels and bronchi. Section through the lung discloses more or less consolidated tissue of an opaque, grayish or yellowish appearance, in which the bronchi may be seen as open spaces or filled with mucopurulent liquid. Little distinction between caseous pneumonia and the tubercles can be made in the center of such an area, but at the edges, where the process is seen in the earlier stages, such distinction may be possible.

At times areas of a fibrinous or cellular pneumonia are formed. These differ from caseous pneumonia in presenting a granular or gelatinous appearance, and in their liability to partial or complete resolution. The process is serofibrinous and cellular in character, and often, though not always, due to secondary infections.

The same tendencies to degeneration and softening, on the one hand, and to the processes of repair, on the other, are seen in chronic pneumonic phthisis as are apparent in the acute form. There is the difference, however, that these changes are less rapid, and that, as a rule, proliferation of connective tissue with the formation of fibrous tissue is more pronounced than in the acute disease.

The degenerative and necrotic processes lead to a most characteristic lesion of tuberculous lungs—the *cavity* (Fig. 247). Cavities are formed either through the dilatation of the bronchioles (bronchiectasis), due to their ulcerated and weakened condition and to the pressure of retained secretions, with subsequent ulceration and breaking down of the surrounding caseous tissue; or, on the other hand, to liquefaction of caseous areas not in connection with a bronchial tube. In the latter case, however, communication with the bronchi is frequently established by extension. A single cavity may grow larger and larger by constant ulcerative processes, in which not alone the caseous tuberculous degeneration

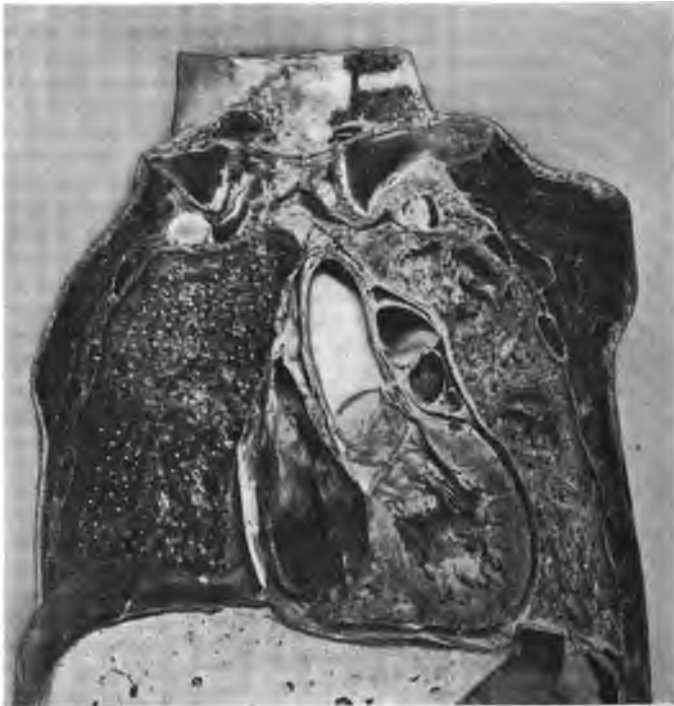


Fig. 248.—Chronic phthisis pulmonalis with cavities of left lung; note communicating cavities near apex, disseminated miliary tuberculosis of right lung (from a specimen in the collection of Dr. G. W. Norris).

takes a part, but also active ulcerative changes dependent upon mixed infection through inspiration of pyogenic organisms. As a rule, however, larger cavities are formed by the confluence of separate smaller ones, and there may be found a series of excavations communicating more or less extensively with each other (Fig. 248). The cavity, or vomica, contains a variable amount of ill-smelling, putrid secretion, consisting of broken-down cheesy matter, pus-cells, degenerated epithelial cells and fibers of elastic tissue, and containing tubercle bacilli, pyogenic organisms, and occasionally mould fungi. The walls of the cavity are generally formed by reparative fibrous proliferation, and are covered

with a "pyogenic membrane," usually darkly pigmented. The inner surface is very rough and ribbed by projecting bands. The latter represent the trabeculæ and blood-vessels of the lung tissue, which have resisted ulceration more obstinately than the surrounding structure of the lung. This resistance may continue to such an extent that the blood-vessel is left as a cord passing directly through the center of the cavity; but, as a rule, the lumen of the vessel is soon obliterated by thrombosis and the vessel itself destroyed. Not infrequently examination of the blood-vessels in the wall of the cavity or passing through it show small aneurysmal dilatations which result from the weakening of the wall by the surrounding necrotic process and from the pressure of the blood within. It is from aneurysms of this character that the large and often fatal hemorrhages of the later stages of tuberculosis take place, though hemorrhage may also occur directly from erosion of blood-vessels without aneurysmal dilatation. The smaller hemorrhages of the early stages of phthisis, which occasion only a streaking of the sputa with blood, are due to early erosion of small vessels of the bronchioles or to capillary ruptures dependent upon congestion.

The reparative processes (connective-tissue formation) in chronic pneumonic tuberculosis may cause cessation of the disease when only limited areas of the lung are affected, by surrounding and thus encapsulating the diseased parts, or by complete fibrosis of the areas. These changes are dominant in the form next to be described.

Fibroid Phthisis.—The reparative or fibrous processes which tend to counteract caseation and destruction may begin before cavity formation or after it. When beginning in the earlier stages the caseous areas will be found to present a capsule of more or less well-developed fibrous tissue, which may completely surround and separate them from the neighboring tissue of the lung. The capsule tends to contract and shrink, and the caseous material within may become completely calcareous. In this manner a limited focus of tuberculosis of the lungs not infrequently becomes completely arrested. When the capsule is not so firm, after a period of quiescence or latency extending over even a number of years, fresh extension may begin, the capsule may be perforated, and acute pneumonic phthisis may be established, or the tuberculous process may extend more slowly through the contiguous areas as chronic ulcerative phthisis. When the tuberculous lesion is limited and consists of minute foci not too closely conjoined, the fibrous tissue proliferation may intersperse the lesion so that the whole is converted into sclerotic tissue instead of being merely surrounded by a capsule.

The fibrous capsules surrounding the cavities, which have already been alluded to, may be of varying prominence. In case of small vomices with pronounced fibrous walls the contraction of the latter may almost obliterate the cavities, leaving only narrow and distorted spaces containing a small amount of putrid material (*cicatrices fistuleuse* of Laennec). Complete healing of a cavity of notable size probably never occurs. When the excavations are of large size the reparative processes consist simply in the formation of a thick wall of fibrous tissue, which

prevents the further extension, for a time at least, of the tuberculous process.

Complications in Bronchogenic Pneumonia.—Of first importance in tuberculosis of the lung is the condition of the pleura. In the acute pneumonic form the pleura adjoining the diseased areas is generally more or less inflamed and may present considerable fibrinopurulent exudation, as in croupous pneumonia. Serous or seropurulent exudation may likewise be present, and eruption of miliary tubercles in the pleura is not unusual. The same processes may occur in chronic pneumonic tuberculosis or chronic phthisis. More commonly there are found simply fibrous adhesions binding the one surface of the pleura to the other, especially at the apex.

Extension of the tuberculous process may also take place directly upward along the air-passages, and is due, for the most part, to direct infection by the sputa. There may thus occur tuberculous ulceration of the larger bronchi, of the trachea, of the larynx, or of the pharynx. When the sputa are swallowed, as is especially likely to happen in children, or in adults during sleep, intestinal tuberculosis is apt to occur.

Finally, dissemination of the tuberculous disease through the blood is frequent. A caseous area adjacent to one of the veins may penetrate the lumen of the vessel and discharge its contents into the circulating blood, or may first occasion tuberculous proliferation in the intima of the vein or infectious thrombosis, from which the blood is secondarily infected. There results general miliary tuberculosis, the tubercles occurring especially in the spleen, the liver, the kidneys, the choroid coat of the eye, or in the membranes of the brain or other serous membranes.

Acute pneumonia may accompany either acute or chronic pneumonic tuberculosis, and certain authors insist that in practically all cases there is more or less mixed infection. This is probably not the case, but complicating pneumonia is undoubtedly frequent. In most of such cases localized patches of catarrhal bronchopneumonia are seen between the caseous lobules; but sometimes a frank fibrinous consolidation may occupy the lower lobe of a lung in which the upper lobe presents beginning tuberculosis. Quite frequently there are small areas of pneumonic consolidation of fibrinous character in the lobe which is itself the seat of tuberculous involvement. Toward the end of life there is usually extensive edema of the bases and posterior portions of the lungs.

The heart has interesting relations with tuberculosis of the lungs. Early writers called attention especially to the fact that phthisical subjects frequently present unusual smallness (hypoplasia) of this organ, and later attention was directed to the fact that congenital stenosis of the pulmonary orifice predisposes to tuberculosis of the lungs. Some have claimed that there is an antagonism between cardiac disease and tuberculosis. This view is not well founded, though it is probable that the chronic congestion of cardiac disease renders the lung somewhat less vulnerable to tuberculous infection than the normal lung. Where

there is a long-standing tuberculous consolidation, hypertrophy, especially of the right ventricle, is likely to occur. Tuberculous pericarditis may be found in association with tuberculous pleurisy; and tubercles may also, though much more rarely, be found upon the endocardial lining. The latter are due to infection through the blood.

Hematogenic Tuberculosis

This form occurs when a focus of tuberculous disease ruptures into a blood-vessel and the infective contents are disseminated in the circulation. As a rule, hematogenic tuberculosis of the lungs is only a part of a general tuberculosis of the entire body. The points from which the primary infection may take place are, of course, numerous, but caseous lymph-glands of the cervical or peribronchial group, or old foci of tuberculosis at the apex of the lung, are perhaps the most frequent. The organs and structures of the body likely to be involved by general hematogenic tuberculosis are the spleen, the liver, the kidney, the choroid coat of the eye, the meninges, and, more prominently than any other organ, the lungs. In the rare cases in which rupture of an old pulmonary focus has occurred into one of the branches of the pulmonary artery, only one lung, or but a part of a lung, may be involved. Some writers think that intimal tubercles of the pulmonary artery and its branches are the sources of continued infection of the lungs. Attention has been previously directed to the probability that in some, if not many, cases what appears to be bronchogenic pulmonary tuberculosis is, in reality, hematogenic, the bacilli having entered the body at some obscure point without causing a lesion at the portal of entrance, and having produced a localized lesion in the lung instead of the more typical disseminated tuberculosis usually found in hematogenous infections.

Pathological Anatomy.—The pathological feature of importance in hematogenic tuberculosis is the formation of miliary tubercles. These appear as gray or translucent areas, the size of millet seeds, around and involving the terminal arterioles or capillaries in the intervesicular septa. At first they may be so small that the naked eye scarcely discovers them, and they are so translucent that oblique light is necessary to make them appear to view. Later, they increase in size and become more grayish and opaque. Microscopically, there are the well-known characteristics of the miliary tubercle embedded in the perivascular connective tissue. These tubercles, however, are prone to distinguish themselves from the characteristic tubercles seen elsewhere by their more irregular outline and the more irregular arrangement of their component histological elements. When the tuberculous process is particularly rapid and virulent, giant cells are few in number, and the tubercle is composed mainly of proliferated connective-tissue cells of the ordinary type, some epithelioid cells, and round infiltration cells, all of them more or less granular, and the entire nodule surrounded by a zone of caseous, catarrhal, or even hemorrhagic pneumonia of the contiguous alveoli of the lung (Fig. 249). The tubercles are rarely seen in the stage

of advanced necrosis, but this may take place in instances of a more chronic course in which the bacteria are admitted to the lungs slowly

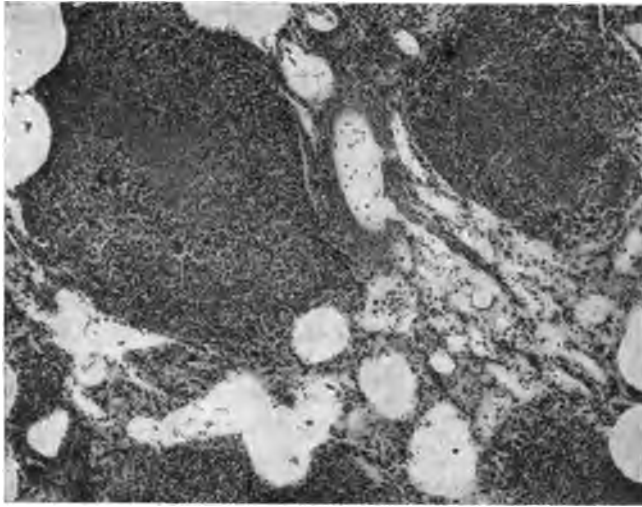


Fig. 249.—Miliary tuberculosis of the lung, showing two tubercles with degenerated centers.



Fig. 250.—Hematogenic tuberculosis, showing many scattered miliary tubercles and several clusters (modified from Bollinger).

and perhaps in a state of lesser virulence than common. In those instances of what may be termed “chronic miliary tuberculosis” there may be a considerable amount of caseation of the tubercles, and the patches,

as a rule, become decidedly larger than in the ordinary acute form (Fig. 250). An explanation of this form of chronic miliary tuberculosis has been offered by certain authors, who hold that these are instances of infection through the thoracic duct and blood-vessels. The infective material enters the thoracic duct from caseous lymphatic glands in the abdomen or thorax, and is discharged with the lymph into the veins in a gradual manner, only a little being allowed to pass at a time.

The ordinary and typical acute miliary tuberculosis presents itself clinically as an acute infectious disease, running its course rapidly and causing early dissolution. The disease is rather a general toxemia than a local process, and toxic changes may be present in various organs, such as occur in other infectious and toxic diseases. The heart, liver, the kidneys, and, in general, the parenchymatous structures are prone to become degenerated, and when the febrile infection continues there may be extensive fatty degeneration. In addition to the eruption of miliary tubercles in other organs, to which allusion has already been made, there is also involvement of the pleura which belongs properly to the pulmonary process itself, and is simply a continuation of the same infection which gave rise to the pulmonary involvement.

Lymphogenic Tuberculosis

It is possible for tuberculous infection of the lungs to occur through the lymphatic channels in several ways. In speaking of acute miliary tuberculosis, particularly of the more gradual type, reference was made to the fact that infective material is sometimes carried by the thoracic duct from the lymphatic glands of the abdomen and posterior mediastinum, as well as possibly from carious thoracic vertebræ to the blood-vessels, and thence distributed through the blood to the lungs as a hematogenic infection. Direct infection, however, through the lymphatic channels may take place. Thus, tuberculous pleuritis, either primary or secondary to tuberculous disease of the vertebræ or ribs, sometimes spreads directly into the lung through the lymphatic vessels traversing the interlobular connective tissue; and in cases of caseous tuberculosis of the peribronchial glands the infective material may be conveyed into the lungs either by a reversal of the current of lymph in the vessels running to these glands or by direct extension along the lymphatic walls. A form of lymphogenic tuberculosis of the lungs may also be referred to in which caseous lymph-glands directly perforate the lung tissue, but the actual dissemination of the process in the lungs in these cases is usually through the bronchial tubes into which the bacilli gain entrance.

Pathological Anatomy.—It is characteristic of lymphogenic tuberculosis to find small nodular areas which microscopically are seen to be more or less characteristic tubercles. These are scattered along the lymphatic vessels running in the interlobular septa or surrounding the blood-vessels and bronchi. In the instances of lymphogenic tuberculosis secondary to pleuritis suppurative lymphangitis and perilymphangitis (see Pneumonia) are not infrequently associated.

SYPHILIS

It has been the occasion of much dispute whether the many forms of pulmonary disease attributed to this cause can be really so classified. Among such doubtful cases are certain pulmonary consolidations in secondary syphilis, and lesions of the lungs in old syphilitics that have the superficial appearances of tuberculosis. Undoubtedly some of the conditions attributed to syphilis are cases of tuberculosis, or of some other form of pulmonary disease. But there are other varieties which can unquestionably be spoken of as syphilitic. Among these are the diffuse infiltration of the newborn and the tertiary gummata.

Diffuse syphilitic infiltration of the lungs is occasionally met with in the newborn. As a rule, infants showing this are stillborn. It manifests itself as a more or less lobar consolidation and induration of the lung tissue. On section, the lung is light gray or almost white in color, and completely airless, so that the name *pneumonia alba*, given by older writers, was highly significant. Microscopically, there are seen widespread round-cell and spindle-cell infiltration and proliferation in the interalveolar and interlobular connective tissues, with more or less compression of the bronchioles and alveoli. The epithelium of the latter may be somewhat proliferated and desquamated, and shows a tendency to fatty degeneration and necrosis. In some instances the degenerative changes do not take place, and the proliferated epithelium of the alveoli is massed within the alveolar lumen, and is, for the most part, of a cuboidal character. The blood-vessels commonly show proliferation of the adventitia as well as of the intima, and may be completely obliterated. According to Birch-Hirschfeld, syphilitic fetuses of the sixth or seventh month sometimes present limited disease of this nature, and of such distribution that it is recognized to begin as a peribronchial and peri-alveolar infiltration of lobular distribution. In this type *Spirochaeta pallida* are very numerous.

Syphilitic gummata may be associated with the diffuse form of congenital syphilis, or may be present in the newborn without the latter. Gummata are occasionally seen in adults. They are present most frequently near the root of the lung beneath the pleura, but may be scattered through other parts of the organ. As a rule, the number is limited. They appear as more or less rounded nodules of a grayish to yellowish color, with more or less fibrous overgrowth surrounding them and often radiating from them into the surrounding lung tissue. Central necrosis may proceed to such extent that cavities are formed.

Occasionally the contents of a gumma may be discharged through the bronchial tubes, or they may be absorbed and a cicatricial puckering of the lung tissue may mark the place of the former disease. *Spirochaeta pallida* can be found, but are not numerous.

Syphilitic fibrous induration of the lung, so-called, has been described, and it seems likely that some of the cases embraced in the description are really syphilitic in nature. The process begins, as a rule,

at the root of the lungs, from which it radiates through the tissue toward the pleura. The fibrous tissue, for the most part, surrounds the bronchi and blood-vessels (Fig. 251). In another group of cases the process spreads from the pleura and occasions the formation of dense bands of fibrous tissue passing inward into the lung structure. In still other cases the fibroid overgrowth is so diffuse that the appearance presented resembles so closely that of pneumonokoniosis that it is practically indistinguishable. It is quite probable that many instances in which appearances such as these are met with are not at all syphilitic; but

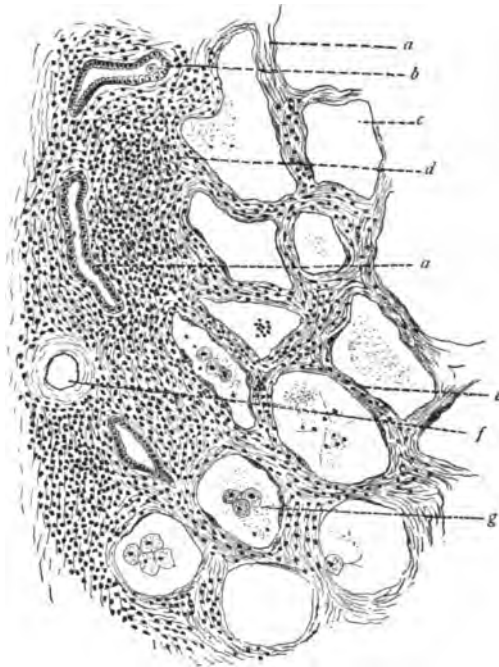


Fig. 251.—Syphilis of lungs: *a, a*, Thickened alveolar walls or stroma; *b*, partly longitudinal section of bronchus; *c*, uninfiltrated alveoli; *d*, new connective tissue infiltrated with small round cells; *e*, cells lining alveoli; *f*, artery showing thickened walls; *g*, desquamated lining cells (Linsley).

the occurrence of changes of this description in association with gummata, and, again, the occurrence of such changes without gummata in undoubtedly syphilitic individuals, make it likely that some at least are of this origin and nature. *Spirochaeta pallida* are exceedingly difficult to find, and only can be found, indeed, where there is a frank infiltrate among the fibrous tissue.

GLANDERS

Glanders occasionally affects the pulmonary tissue, the infection taking place either by inhalation from ulcerated lesions in the nose or other portions of the upper air-passages, or, more rarely, by distribu-

tion of the bacilli through the blood. The lesions are of two kinds. There may be merely a grayish or purulent infiltration of a diffuse character, with the formation of abscesses and often with associated hemorrhagic infiltration. Considerable areas of the lung may be consolidated in this manner, or the process may be localized and lobular. In other cases nodular patches varying from the size of a hemp-seed to that of a pea are seen in various parts of the lung. These consist of masses of round cells, and show an early tendency to degeneration. More or less hemorrhagic and catarrhal inflammation of the alveoli surrounding these nodules may be present.

ACTINOMYCOSIS

Actinomycosis is a rare affection of the lungs. It may result from the direct extension of actinomycosis of the lymphatic tissues and cellular structures in the anterior or posterior mediastinum, when there are formed in the pulmonary tissue fistulous necrotic tracts containing more or less cheesy and purulent material, in which the characteristic yellowish actinomycosis granules are found. The latter, on microscopical study, show the actinomycetes. The infection may also take place by a gradual descent of the process from the mouth or upper respiratory passages along the trachea and bronchi to the lung; or, more commonly still, by aspiration of the infective agents. In the latter cases nodules consisting of round cells are formed, and present themselves as grayish or grayish-red patches varying in size from that of a pea to that of a cherry, and showing a decided tendency to fatty degeneration and purulent softening. The surrounding lung tissue is commonly consolidated, and presents the appearances of purulent and catarrhal or even hemorrhagic pneumonia. In many cases there is also a manifest tendency to productive changes, which lead eventually to the formation of more or less fibrous tissue within the alveoli and in the interalveolar and interlobular connective tissues. Not rarely this indurative process completely surrounds areas of degeneration and softening. Infection with streptothrix follows the same general character.

TUMORS

The lungs are, comparatively speaking, rarely the seat of tumors, though a variety of both primary and secondary growths occur.

Connective-tissue Tumors.—Small nodular *fibromata* have occasionally been observed scattered through the lungs in the peribronchial connective tissue, and a few instances of similar nodules of *lipoma* are recorded. *Chondroma* is more common than either of these, and doubtless takes origin from the bronchial cartilages. Secondary chondromata have been observed in cases of chondroma elsewhere. True *osteoma* is rare, but more frequently ossification of sclerotic areas is met with in instances of pneumonokoniosis.

Sarcoma is the most frequent connective-tissue tumor of the lungs.

The lymphosarcoma form may originate in the lymphatic glands surrounding the bronchi at the roots of the lungs, from the lymphatic nodes surrounding the smaller bronchi within the lungs, from the lymphatic vessels themselves, or from the subpleural or other connective tissue of the lung itself. Primary sarcoma is less common than secondary. In one form it presents itself as rounded masses of grayish or yellowish color lying around the bronchi in the root of the lung (Fig. 253). On section through this it is seen to consist of more or less enlarged and transformed lymphatic glands, and there may be secondary nodules scattered through the lung. This form of sarcoma is particularly common in pneumonokoniosis, as seen in the fibroid lungs of the cobalt-miners of Schneeberg. Primary sarcoma may also be of the form called *endothelioma*, arising either within the lung tissue or from the pleura. The lymphatic vessels in the peribronchial tissue become filled with proliferated cells, and their ramification may be distinctly visible on section as a network traversing the pulmonary tissue. Primary sarcoma of the spindle-cell or round-cell variety may spring from the subpleural connective tissue. Giant-cell sarcoma has been observed.

Secondary sarcoma is extremely common. It is seen in nearly all instances in which metastasis has occurred from a primary growth in any part of the body. In these cases there are found well-defined nodules of varying size, situated for the most part near the surface of the lung (Fig. 254). They are whitish in color and tend to soften. The lung tissue between may be congested, and there may even be pneumonic consolidation. Secondary sarcoma of the lung may also occur from direct extension of mediastinal sarcoma or of sarcoma in other of the surrounding structures. An interesting type of secondary involvement of the lungs by sarcoma or a process resembling sarcoma occurs in "malignant lymphoma" or "lymphadenoma," either with or without leukemia. These may be considered as allied to generalized lymphosarcoma. The lungs are found to contain small nodules, consisting of round cells without stroma or embedded in a more or less reticular matrix of stellate and spindle cells.

Epithelial Tumors.—*Carcinoma* is practically the only form to be considered, though *adenoma* of the lung has been described. Carcinoma of the lung is certainly less frequent than was formerly believed, sarcoma



Fig. 252. — Sarcomatosis of lung, hematogenous in origin, showing distribution from hilus.



Fig. 253.—Lymphosarcoma of the postbronchial glands, invading the lung; the lung is divided by a long incision and the halves laid open.



Fig. 254.—Secondary sarcomata of the lung: the primary growth was attached to the pleura.

having been confused with it. Massive cancer may start from the mucous glands of the larger bronchi near the root of the lung. The



Fig. 255.—Secondary metastatic lymphosarcoma of lung (from a specimen in the collection of Dr. Allen J. Smith).



Fig. 256.—Metastatic carcinoma of lungs from a primary pyloric growth (photograph by Dr. Ayer).

tumor is irregular, soft, and tends to ulcerate in the center, forming cavities. Secondary nodules within the lung tissue are seen along the

lymphatic vessels surrounding the bronchi. Primary carcinoma may also start from the epithelium of the finer bronchial tubes. The proliferation soon penetrates the wall of the bronchus and extends along the lymphatic vessels in the peribronchial connective tissue. In this manner bands of new growth are seen traversing the lung. Occasionally squamous-celled carcinoma may originate in the epithelium of the terminal bronchioles and alveoli.

Secondary carcinoma of the lungs is less frequent than secondary sarcoma. It may occur by metastasis from cancer elsewhere, and in these instances the appearance of the nodules is much the same as that of sarcoma. Secondary cancer of the lung may also result from extension of esophageal carcinoma or of cancer of the breast penetrating the thoracic walls and pleura. Finally, in carcinoma of the upper respiratory passages or of the mouth, inhalation of cancerous particles may lead to secondary nodules in the lungs, associated at times with areas of bronchopneumonia.

Cysts.—Congenital cysts have been described, but they are probably merely dilatations of the bronchi. (See *Bonchiolectasis*.) Adenomatous proliferation of the epithelial lining of such dilatations may take place. Dermoid cysts are rarely encountered. They may discharge through the bronchial tubes.

PARASITES

Besides the specific and pathogenic micro-organisms that have been referred to as occurring in tuberculosis, pneumonia, and other infectious diseases, various forms of bacteria and mould fungi are met with as accidental and non-specific parasites. Such micro-organismal collections are most frequent in areas of gangrene, in degenerated infarcts, and in dilated bronchi or tuberculous cavities. *Sarcinæ*, *leptothrices*, *streptothrices*, and several varieties of *aspergillus* have been noted. The general term *Pneumomycosis aspergillina* is applied to the occurrence of the last-named mould fungi in the lungs. Sometimes they are so abundant that they are readily discovered in the sputa; and it is likely that certain inflammatory conditions of the lungs are directly due to such organisms. The clinical course may suggest tuberculosis, and pathologically diffuse or irregular consolidation of the lungs may characterize such cases. (See p. 324.)

Animal Parasites.—Of the lowest forms of animal life or protozoa, the *Monas lens*, *cercomonas*, and *paramecium* have been observed. These are entirely accidental, occurring in cases of gangrene, putrid bronchitis, and similar conditions. The class of *Vermes* furnishes the more important parasitic affections of the lungs. The *Paragonimus westermanii* is not infrequent in parts of Asia. It occasions serious hemoptysis. The *Strongylus apri*, echinococcus cysts, and *Cysticercus cellulosæ* are occasionally seen. *Linguatula rhinaria* has been observed.

THE PLEURA

Anatomical Considerations.—The pleura is a membrane composed of fibrillar connective tissue and elastic fibers, containing a rather abundant network of capillaries. It is lined on the surface with a single layer of flat endothelial cells, between which there are openings from the pleural cavity into the subpleural lymphatics. The latter form a rich network in the subpleural connective tissue and play an important part in the pathological processes affecting the pleura. It must be remembered that the two pleural surfaces are normally in apposition, that is, no cavity exists. They move over one another with the movements of the chest.

CIRCULATORY DISTURBANCES

Active Hyperemia.—This arises as the early stage of inflammation or as the result of decrease in tension, such as occurs when fluid in the cavity is removed.

Passive hyperemia occurs in various diseases interfering with the respiration, and still more intensely in cases in which there is pressure upon the azygos veins or diffuse intrathoracic pressure.

Petechial hemorrhages may occur when the congestion is intense. They are particularly frequent and prominent in cases of death from suffocation, but are also seen in various disorders of the blood and hemorrhagic diatheses, such as pernicious anemia, purpura, and intoxications of various kinds.

Hemothorax is the term applied to the presence of free blood in the pleural cavity. It may be due to wounds of the chest wall, causing rupture of blood-vessels, to fracture of the ribs, and to rupture of aneurysms into the pleural sac. In some cases the etiology is obscure. If the pleura is in a healthy condition and secondary infection does not take place, more or less rapid absorption of the blood ensues. When infection occurs, secondary inflammations of the pleura and disorganization of the blood result.

Hydrothorax, or dropsy of the pleural cavity, may be but a part of a general edema occurring in chronic kidney or heart disease. It is usually bilateral, and the fluid presents the ordinary characteristics of a serous effusion. Unilateral hydrothorax is, however, not infrequent in cardiac disease attended with great enlargement of the organ. The hydrothorax in such cases is generally right sided, and is probably due, according to Fetterolf and Landis, to pressure by some dilated segment of heart upon the pulmonary veins which drain those from the visceral pleura. The pleura itself is not particularly disordered, but very frequently some opacity and loss of luster is noted, and there may be edema of the subpleural fibrous tissue. The lungs are pressed backward toward the root and against the spinal column, and may be considerably compressed. Unilateral hydrothorax may be due to pressure upon the veins of one side by tumors or aneurysm. A small amount of serous outpouring into the pleural sacs occurs quite commonly just

prior to death. The fluid of hydrothorax has the usual characters of transudates, low specific gravity, pale color, alkalinity, moderate protein content, and very low cell content.

Chylous effusion in the pleuræ is due to obstruction or rupture of the thoracic duct or some large lymphatic channel, with the appearance of a milky opaque fluid containing fat-droplets.

Hydrothorax causes compression of the lungs and displacement of the other adjacent viscera. The seriousness of the results are in proportion to the amount of effusion.

Pneumothorax designates the presence of air in the pleural cavities. It may result from rupture of tuberculous vomicæ, gangrenous areas, softened hemorrhagic infarcts, or abscesses of the lungs, or rupture of emphysematous air-vesicles beneath the pleura, allowing egress of air into the pleural sac. It may also occur after an empyema has ruptured into the lung and established a fistulous communication between the pleural sac and the bronchioles. Very rarely it is due to a penetrating wound of the chest. The pleural sac may be more or less tensely distended with air; the lung collapses against the spine, is more or less grayish or brownish in color, indurated, and airless. The pleura itself may present no abnormality, and the air may be absorbed; but very frequently infection takes place, and purulent exudation from the pleura collects in the sac. The condition is then spoken of as *pyopneumothorax*. The neighboring organs are often greatly displaced, particularly the heart, the diaphragm, and the liver. In left-sided pneumothorax the heart may be pushed far to the right of the sternum, and when the right side is affected the liver may be pushed downward considerably below the ribs. The condition of the air inlet and outlet has something to do with the outcome of the condition. If the fistulous channel from a lung cavity permits air only to pass to the pleura with inspiration, and does not permit its escape upon expiration, the accumulation will continue. The air, once within the cavity, may remain in about the original amount, or it may undergo variations when a free ingress and egress is afforded. Pneumothorax may be circumscribed by pleural adhesions, and then is termed "closed."

INFLAMMATION

Inflammation of the pleura, or pleuritis, is designated by the clinical name *pleurisy*.

Etiology.—It may result from local or from general causes. Among the local causes the most important are extension of inflammation from the lungs in the various forms of pneumonia, in gangrene and tuberculosis; extension from pericarditis or mediastinal diseases, and extension from inflammatory affections of the spine, of the ribs, or of the chest walls. Less directly, peritonitis, hepatic abscess, and other abdominal affections may occasion pleuritis by extension, and in rare cases perforation of esophageal or gastric ulcers, or abscess of the spleen or liver, may be the cause.

In the group of cases due to general causes the pleural inflammation is the result of infection or intoxication involving the pleura through the blood. Thus, in pyemia and septicemia, in rheumatism and in other acute infectious diseases, and in Bright's disease, acute inflammation of the pleura is not uncommon. Cold and traumatism have long been regarded as important causes, but their action is doubtless only a predisposing one, the immediate cause being some infection for which the traumatism or the exposure to cold has paved the way.

It is to be remembered that the pleura is made up of a visceral and a parietal layer, two smooth surfaces bathed by a small quantity of lymph, sliding over one another in respiratory movements. While the inception of pleurisy may be localized the process soon spreads over both surfaces. It is, of course, possible to have an acute or chronic pleurisy localized by reactive connective-tissue growth, as when due to a purely local cause, such as an indented broken rib.

The micro-organisms found in pleurisy are quite numerous. In the cases secondary to ordinary pneumonia, pneumococci are frequently discovered, and these micro-organisms may be present even though there be no pneumonia at all. In the instances secondary to tuberculosis of the lungs, as well as sometimes in cases of primary pleurisy without affection of the lungs, tubercle bacilli are discovered. It is important to note the fact that in many instances a small and unrecognized tuberculous lesion of the lung may be the source of infection in cases which seemingly are primary pleurisies due to exposure, cold, etc. It would, however, be a mistake to assume that all of such apparently primary pleurisies have a tuberculous etiology. In the purulent cases, as well as in some instances of simple fibrinous or serofibrinous pleurisy, staphylococci and streptococci are detected. When there is abundant liquid it is always difficult to discover the micro-organisms, and in many instances in which bacteria have not been found it is probable that the difficulty of their demonstration, even by animal experimentation, rather than their absence, accounts for the failure to demonstrate them. In rare instances the *Bacillus coli communis*, the typhoid bacillus, the bacillus of anthrax, and other organisms have been found.

Pathological Anatomy.—Several forms of pleuritis may be recognized, though one of these merges into the other, and a single case may pass from one into another form at its various stages. It is well, however, to separate these stages as distinct forms, since many cases maintain a uniform character throughout. The forms are the *fibrinous*, *serofibrinous*, *purulent*, and *hemorrhagic*; after any of these forms there may be left chronic pleural thickening or adhesions of a fibroid character.

Fibrinous pleuritis begins with congestion and loss of luster of the pleural surface, after which there soon follows exudation of a fibrinous character, forming a thin, whitish pellicle on the surface. This may become yellowish and increase in thickness, so that the pleural surfaces become agglutinated, and when separated present an appearance likened to the appearance of two pieces of buttered bread separated after

having been pressed together (*bread-and-butter pleurisy*). This process may be confined to small areas of the pleura, or it may be quite universal. Sometimes it is limited to the reflections of the pleura separating the lobes of the lung.



Fig. 257.—Transverse section of lung from a case of pleuropneumonia, showing great thickening of the pleura (A) and consolidation of one of the lobes of the lung (B).

Microscopically, the exudate consists of fibrils or flakes or granular masses of fibrin more or less infiltrated with round cells. Beneath this the endothelium of the pleura is found to be somewhat thickened by proliferation and some of the cells are detached. Two conflicting views have been entertained regarding the origin of fibrin formation in the

pleura. According to one, the deposit is purely exudative and the endothelium is in nowise involved, being found intact under the fibrinous layer. According to the other view the fibrin formation is partly dependent upon destruction of endothelial cells. Whichever explanation is correct, there almost always remains a broken layer of endothelial cells in the acute and subacute stages. This may be removed when adhesions and chronic thickening obliterate the membrane. The connective tissue beneath the endothelium and the subpleural connective tissue are infiltrated with round cells and the blood-vessels are hyperemic. In favorable cases and when the process has been slight a gradual reabsorption of the exudate takes place, and the integrity of the pleura may be restored completely. When the exudate has been more extensive and the agglutination of the pleural surfaces has been considerable, new blood-vessels from the capillaries of the pleura penetrate the fibrinous exudate, fibroblastic cells develop from the older connective-tissue cells, and gradually organization takes place, so that the adjacent layers of pleura are bound together by connective tissue, the fibrinous exudate gradually undergoing absorption and disappearing. The adhesions thus formed are at first delicate and quite cellular, but are later converted into dense, sclerotic bands. When fibrinous pleurisy occurs repeatedly, as in tuberculosis of the lungs, and is not sufficiently extensive to cause adhesions, the surface of the pleura may become thickened and opaque in spots from proliferation of the connective tissue. In this way considerable chronic thickening of the pleura may ensue.

Serofibrinous pleuritis may be simply a further stage of the foregoing form, though in many instances it begins almost at once as a serous exudation into the pleural sac. The liquid is heavier than dropsical fluid and contains flakes and shreds of fibrin. Microscopically, it is found to contain white and red blood-corpuscles in small numbers, and occasionally detached endothelial cells. Sometimes the number of red corpuscles increases considerably, and there may be a gradual transition to the hemorrhagic form of pleuritis. The amount of liquid varies from a few cubic centimeters to several liters; and the pleura itself shows a more or less extensive coating of fibrinous exudate. The lung is pressed backward, as in pneumothorax or hydrothorax, and the adjacent organs (heart, liver) are displaced.

Purulent pleuritis, empyema, or pyothorax, is always the result of micro-organismal infection. The process may begin as a purulent pleuritis, or as a primary serofibrinous pleurisy, secondary pyogenic infection occurring either from within the body or through infected aspirating instruments from without the body. It may supervene upon pneumonia, tuberculosis, or abscesses in adjacent parts (subdiaphragmatic). When a transition of the latter kind occurs the exudate is seen to become more and more turbid; the number of pus-corpuscles gradually increases until the liquid is quite purulent. Spontaneous discharge of empyema may occur and most frequently takes place through the lung and bronchi. More rarely rupture occurs through the chest walls anteriorly between the ribs. When rupture has occurred through the

lung and bronchi the fistulous communication may remain open and pneumothorax may ensue.

The pleura in empyema shows more or less abundant granulations, which in case of discharge of the liquid serve eventually to unite the costal and pulmonary pleura by firm fibrous adhesions. Occasionally the pus may be completely absorbed, or it may undergo gradual inspissation, remaining as a more or less cheesy detritus, which may finally become calcareous. Such terminations, however, are rare. Again, the adhesions may surround an area of much compressed lung and enclose the exudate over this area. Thus, we have encapsulated pleurisy. In the healing of empyema, retracting scars are common, with the result that the lungs, chest wall, or both are distorted.

Hemorrhagic pleuritis is generally the result of tuberculous infection or of malignant disease of the lungs and pleura. Pleuritis may also take a hemorrhagic form in old and cachectic individuals, or in persons suffering from scurvy, purpura, and similar diseases. As a rule, the liquid is serous, with considerable admixture of blood, but in tuberculous and malignant pleuritis it is sometimes well nigh pure blood.

Chronic Pleural Thickening.—This term is used to include cases of thickening of the pleural membrane following various forms of acute pleurisy, and also cases of a progressive productive character. To the latter alone the term *chronic pleurisy* is, strictly speaking, applicable. In either case the pleura is thickened by fibrous overgrowth, sometimes uniformly, at other times in the form of localized thickenings or adhesions. The subpleural pulmonary tissue may become implicated. Eventually, the thickened pleura contracts, and if adherent to the chest wall may cause retractions. The pulmonary tissue is compressed and the bronchi not rarely become distorted. In either primary or secondary chronic pleuritis there may be a total obliteration of the pleural cavity. The pleura becomes thick, opaque, and is poorly supplied with blood-vessels. Cartilaginous or calcareous change may occur.

Associated Lesions in Other Parts.—Though pleuritis is frequently the result of acute or chronic affections of the lung, it often occasions secondary disorders in the latter organ. The subpleural lymphatics are commonly distended with cells, and the inflammatory process may extend for considerable distances along these channels into the interlobular septa of the lung. In empyema the resulting purulent lymphangitis and perilymphangitis lead to striking pathological appearances (see Pneumonia). The lung also suffers from direct pressure in serous and purulent pleuritis. If the compression to which it is subjected is not relieved by absorption of the liquid or by its removal by aspiration, the alveolar epithelium degenerates and proliferative inflammation takes place in the connective tissue, so that a permanent contraction of the lung results. The removal of the liquid at this stage is not followed by the return of the lung to its proper size and function. On the contrary, the removal or absorption of the liquid in these cases, especially when they occur in young children, causes a sinking in of the ribs and curvature

of the spinal column, and the heart and other adjacent organs may be permanently displaced. Most remarkable deformities of the chest may occur. Less extensive contraction of one side of the chest, or displacement of the heart, may result from the contraction of bands of adhesions, without marked collapse of the lung.

Pathological Physiology.—Acute pleurisy occasions marked local symptoms, beginning with sharp pain on the side affected. This is usually due to the local inflammation and rubbing of the affected parts. There may, however, be extensive neuralgic pains radiating from the center of infection. With the development of effusion, the pain, as a rule, subsides, as does also the irritative cough which attends the first stage, but shortness of breath develops in correspondence with the amount of effusion. Very extensive effusion in the chest may, however, cause even more marked pain and tenderness than dry pleural inflammation. The infection in simple pleurisy seems to be a mild one, as fever and constitutional symptoms are rarely marked. Sometimes the temperature is a fluctuating one, and sweating and constitutional depression further suggest suppuration, though the effusion is purely serous. Irregular fever and constitutional symptoms of the kind indicated are habitual in empyema.

INFECTIOUS DISEASES

Tuberculosis of the pleura, or tuberculous pleuritis, may be either primary or secondary. Cases of the former are comparatively rare. In most instances the pleural disease is secondary to tuberculosis of the lungs or to tuberculosis of other adjoining parts. Hematogenic infection may occur under the same conditions as hematogenic infection of the lungs, and frequently the lungs and pleuræ are studded with miliary tubercles at the same time.

When the pleural disease is secondary to tuberculosis of the lungs the appearances vary considerably. In many cases small gray or yellow tubercles are found in the subpleural connective tissue and in the pleura, and the surface may be coated with fibrinous exudate, while the cavity of the pleura may be more or less distended with serofibrinous, hemorrhagic, or purulent liquid. Not rarely the liquid effusions are reabsorbed and dense adhesions are formed, or great thickening of the pleura results. Sometimes considerable calcification of the thickened pleura and of the inspissated exudate is the terminal result. The tubercle bacilli are often difficult to demonstrate in the liquid, even by injections into animals, though they may be present in the pleura itself.

Syphilis of the pleura is a doubtful condition. Fresh pleuritis may be found in the neighborhood of a syphilitic gumma; and there are cases of considerable pleural thickening in syphilitic persons in which the disease may possibly be syphilitic, though in these cases, as in similar indurative conditions in the lungs, there is considerable doubt as to the essential nature of the disease.

TUMORS AND PARASITES

Tumors of the pleura are comparatively rare. *Fibromata* and *lipomata* are occasionally seen as small nodular masses in the serous or subserous coat of the costal or visceral pleura. *Chondromata* and even *osteomata* have been observed. More frequently calcification and ossification of portions of the thickened pleura take place after pleuritis.

Primary *sarcoma* may spring from the subpleural connective tissue, and, according to Coats, is especially common in children, and is most frequently of the spindle-cell variety. Primary *endothelioma* of the pleura (Fig. 258) has been studied by a number of investigators. In a case under the observation of one of us it presented itself as a more or less uniform



Fig. 258.—Endothelioma of pleura.

thickening of the pleura of one side, involving the diaphragmatic reflection in particular. The cavity was filled with hemorrhagic fluid and there were some nodular enlargements on the surface (Figs. 259 and 260). This is the usual appearance presented. Metastasis may occur in the lung beneath the diseased pleura, or even in more distant parts. There is a tendency for pleural endothelioma to be accompanied by fibrosis, and oftentimes adhesions are seen.

Secondary tumors of the pleura may occur by metastasis or by direct extension. In the former manner *sarcomata* and *carcinomata* sometimes involve this structure; by the latter method of involvement mammary tumors and new growths of the mediastinum, the ribs, or other adjacent structures may extend to the pleura.

Parasites.—Echinococcus cysts may originate in the subserous connective tissue of the costal or the visceral pleura, and may rupture into



Fig. 259.—Endothelioma of pleura: the pleural cavity was distended with effusion, and the lung was compressed and invaded by secondary nodules.

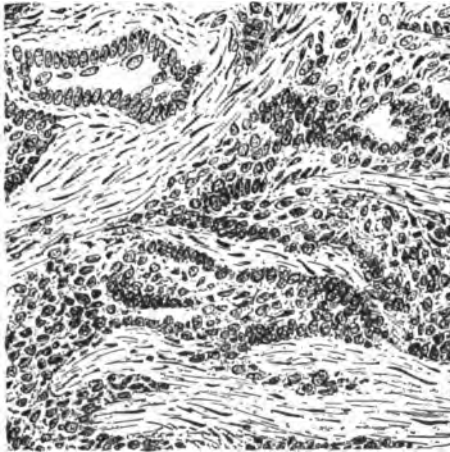


Fig. 260.—Microscopical section from Fig. 259.

the pleural cavity. Psorospermiae have been found in pleural effusions. The dysenteric ameba has been found in the pus of empyema following hepatic abscess.

CHAPTER V

DISEASES OF THE GASTRO-INTESTINAL TRACT

THE MOUTH

CONGENITAL ABNORMALITIES

THE most frequent defects in the development of the mouth are *cleft palate* and *harelip*. In the former of these the entire hard palate may be divided, generally to one side of the middle line; and there may be associated harelip and fissure of the soft palate. Anteriorly, the division occurs between the superior maxillary bone and the intermaxillary bone, the fissure of the lip being also to one side and often extending into the nostril. The soft palate is divided along the middle line, and the uvula may be separated into lateral halves. The lip may be cleft on both sides, so that there is a small central portion connected with the septum of the nose and separated from the lateral portions of the lip. Harelip is more frequently unassociated with cleft palate.

Complete absence of the lips, or unusual shortness, especially of the upper lip, excessive largeness of the mouth by extension of the fissure outward toward the ear, and imperfect development of the lower jawbone, are rare congenital conditions.

Macrocheilia (large lips), macroglossia (large tongue), and ankyloglossia (tongue-tie) are congenital malformations.

CIRCULATORY DISTURBANCES

Anemia of the mucous membranes of the mouth is seen in cases of general anemia, and is often one of the most striking evidences of that condition. It is particularly noticeable in the lips.

Hyperemia.—*Active hyperemia* occurs in the early period of various inflammations, or as a forerunner of some infectious diseases not localized to the mouth; while *passive hyperemia* is met with as the result of obstruction of the circulation in pulmonary and cardiac diseases.

Hemorrhages in the form of small petechiæ occur in purpura and other hemorrhagic diseases, and sometimes in infectious fevers.

INFLAMMATION

Inflammation of the mucous membrane of the mouth is termed *stomatitis*; inflammation of the tongue is designated by the name *glossitis*.

Stomatitis may be of varying character and intensity.

Catarrhal stomatitis may result from direct irritation by hot liquids or chemical substances, or may occur in depressed conditions of the general system, possibly as a consequence of infection. It is more common in children than in adults. The mucous membrane of the mouth is red and usually covered with considerable liquid exudation. When the inflammation is intense, small vesicular cysts may form from distention of the mucous glands, and even localized erosions may appear. When the inflammation has continued for a long time, or has been repeated, there may form upon the surface silvery-white, slightly elevated spots, which result from a hyperplasia of the epithelium, a form of *keratosis*. This condition has been designated by the name of *leukoplakia*.

Mild catarrhal conditions of the mucous membrane of the mouth are especially common on the tongue, the epithelium of which constantly desquamates. In the course of gastro-intestinal and other diseases the desquamation may be more active, the cells, however, being retained upon the surface. Portions of food and bacteria cling to the masses of desquamated cells, and in this manner the whitish or brownish *furring of the tongue* so commonly met with in various diseases is formed. Sometimes the heaping of epithelial cells takes place in localized areas, and extends in peculiarly irregular patches, which, from their resemblance to maps, have given rise to the term "geographical tongue." In chronic cases the whitish spots of leukoplakia alluded to above are formed.

Aphthous stomatitis occurs in children under conditions of mal-hygiene and debility, or as a result of gastro-intestinal and other diseases. Local irritation often plays an important part. There appear in the mucous membrane, especially of the lower lip and gums, small whitish spots lying upon an inflamed base. Usually these are separated, but sometimes confluence occurs, though there is rarely extensive spreading. The whitish membrane covering or constituting the spots is composed of degenerated epithelium, and sometimes of fibrin, so that the term "croupous stomatitis" may in some cases be applied. The lesions are superficial and rarely lead to actual ulceration. It has been held that the preliminary lesion is a vesicle; this, however, does not appear to be frequent, and is certainly not essential.

Foot-and-mouth Disease.—A similar affection occurs in animals, particularly in cows, sheep and goats, and is designated foot-and-mouth disease. This condition is contagious, and considerable epidemics have occurred among persons drinking the milk of infected animals. The specific cause is unknown; the virus is ultramicroscopical and filterable. The process is one of hyperemia and thickening of the corium with vesicle formation in the epithelium. These may rupture and form shallow ulcers.

Bednar's aphthæ are small ulcers found in the mouths of sucking infants and situated at the lateral portions of the palate over the ends of the pterygoid processes, on other parts of the hard palate, or occasionally on the soft palate. They are probably caused by traumatism occurring in the act of sucking.

Ulcerative stomatitis may be met with in various parts of the mouth, especially in the gums. In young children it is frequently the result of malnutrition and lack of cleanliness of the mouth. Various saprophytic micro-organisms normally found in the mouth may, under suitable conditions, aid in the production of ulcerative stomatitis. Among these the *Leptothrix buccalis*, *Indococcus vaginatus*, *Bacillus maximus buccalis*, *Spirillum sputigenum*, and *Spirochæta dentium* have been isolated. Pyogenic cocci may also play a part in its etiology. In various cachectic diseases, particularly in scurvy, the gums become soft and spongy and tend to ulcerate. Mercurial and other forms of poisoning may lead to extensive ulcerations. Deeper ulcerations are found upon the sides of the tongue or the inner part of the lip in cases of injury due to the sharp edges of broken or carious teeth. Ulcerative stomatitis may be secondary to necrotic conditions of the bones or suppurative inflammations about the roots of teeth. Ulceration beneath the tongue is met with in many cases of whooping-cough, and is due to the irritation of the teeth in the paroxysms of coughing.

In ordinary cases of ulcerative stomatitis the gums at the junction with the teeth become reddened and soft, and may present hemorrhagic infiltration. Later, the epithelium of the surface is destroyed and open ulcers result. Considerable suppuration may occur, and the teeth may be loosened and dislodged.

A form of disease about the necks of the teeth and secondarily involving the gums has been termed *pyorrhea alveolaris*. The process is one of cementitis and pericementitis with a separation of the cementum from the lining of the alveolar socket. The cementum is thus deprived of its nourishment normally supplied by this periodontal membrane. The discharge of pus from the gums surrounding the teeth gives the disease its name. It has been ascribed to infection with spirochetes, anaërobes, and amebæ, especially the *Endamæba buccalis*. The importance of the last is strengthened by the fact that pyorrhea is improved by the use of emetin. This condition has been viewed by some as a focal infection from which, as a source, bacteria and their products are swallowed or transferred by the blood to other organs, and there set up intoxications or infections. Thus, arthritis deformans, chronic adenopathy, and aspiration pneumonia are supposed to arise sometimes.

The method of origin of pyorrhea alveolaris is probably that tartar collects upon the teeth down to the gingival margin, below which food particles collect and infection occurs. This process, having at best a very limited outlet, turns to a purulent inflammation, leading to gingivitis and retraction of the gums.

Pseudomembranous stomatitis is most frequently due to the action of the bacillus of diphtheria, and is, therefore, strictly speaking, diphtheria of the mouth. It is usually secondary to pharyngeal diphtheria, but may occur primarily upon the lips or other parts of the mouth. In some cases of aphthous stomatitis the lesion is, in reality, a pseudomembranous one.

Phlegmonous stomatitis is more common in the lips than in other

parts of the mouth, and may be the result of traumatic injuries with intense infection, or a secondary condition after facial erysipelas or other cellular inflammations of the face. The lips and cheeks may be greatly swollen, and suppuration may occur, forming abscesses which tend to rupture into the mouth. A chronic form of inflammation of the deeper tissues of the lips may lead to hypertrophy. This is especially common in the upper lip as the result of long-standing coryza or eczema.

Gangrenous stomatitis, or **noma**, affects the mucous membrane of the cheeks, and occurs in ill-nourished children, especially after measles and other infectious fevers. There is formed a sloughing ulcer on the inner side of the cheek, and inflammatory induration involving



Fig. 261.—Case of noma (Children's Hospital).

the entire thickness of the cheek. The skin at first presents a dark-red or bluish discoloration, and later extensive destruction (gangrene) may occur (Fig. 261). The pathological changes are those of a rapid necrosis of all the tissues, and micro-organisms of suppuration and saprophytes are usually present. Pseudodiphtheria bacilli have been found in some cases. Various spirochetes have been observed. The most common finding is a micro-organism belonging to the necrosis bacilli, but its pathological importance is not established. Putrefactive changes cause a fetid odor. Intense septic infection and intoxication generally attend.

Milder forms of gangrenous stomatitis affecting the gums around carious teeth are occasionally observed.

Associated Conditions in Stomatitis.—In many cases the inflammation may extend from the mucous membrane of the mouth posteriorly to the pharynx. Very commonly the lymphatic glands of the neighborhood are involved, with enlargement of the submaxillary or even the cervical glands. In some cases, especially in mercurial stomatitis, the salivary glands are coincidentally or consecutively swollen and inflamed. Increased flow of saliva (ptyalism or sialorrhea) is a frequent symptom. In intense cases, especially in gangrenous stomatitis, parenchymatous degenerations of other organs may result from general toxemia.

Glossitis.—Superficial catarrhal inflammations have been referred to. The tongue may be involved in the various forms of stomatitis and shows similar changes. More extensive inflammations of the tongue, leading to *parenchymatous glossitis*, may result from injuries, especially when accompanied by infection. The entire organ may in these cases be swollen, and there is round-cell infiltration with a tendency to suppuration. Localized parenchymatous glossitis with ulceration may occur from injury by carious teeth.

Hemilateral glossitis, sometimes attended with the formation of herpetic vesicles, is occasionally observed, and is probably dependent upon disease of the *chorda tympani* nerve.

ATROPHY AND DEGENERATIONS

Atrophy of the muscles of the tongue and cheeks may occur in association with nervous diseases (bulbar palsy). Physiological atrophy of the gums follows loss of the teeth in old age.

Degenerations of the mucous membrane usually accompany inflammations.

Under the name of *nigrities*, or *black tongue*, is described a form of hypertrophy of the papillæ of the tongue with pigmentation. The dorsum of the tongue may be covered with a hair-like coating of dark-brown or blackish color. The cause of this affection is obscure.

INFECTIOUS DISEASES

Thrush, or **parasitic stomatitis**, is met with in young children, and is due to the action of a micro-organism known as *Oidium albicans*. There are formed upon the mucous membrane white patches resembling curdled milk, and varying in size from mere points to large areas. These tend to coalesce and to spread. The mucous membrane is reddish and inflamed. The back and sides of the tongue and the inner parts of the cheeks are favorite seats. Microscopically, the white coating is composed largely of mycelial threads of the parasite, with which are mingled degenerated epithelial cells and generally also other micro-organisms, notably micrococci. The process may extend to the pharynx, and sometimes as far as the bronchi or the stomach, through the larynx and esophagus.

Tuberculosis of the mouth may be primary or secondary. The latter is especially frequent at the root of the tongue, and is secondary to tuberculosis of the larynx or pharynx (Fig. 262). Small nodular masses of tubercles are formed, and tend to undergo cheesy degeneration, forming ulcerated areas. Primary tuberculosis leading to ulceration may occur upon the lips or upon the tongue as a result of direct inoculation, as in the kissing of a tuberculous person. Nodular masses are formed, which at first present themselves as papillary elevations, but subsequently undergo characteristic necrosis. Tuberculous ulcers are usually irregular or undermined, and the bases are more or less caseous and infiltrated by tubercles. The injury of the tongue by the teeth, and the favorable soil offered for the retention and multiplication of the micro-organisms in carious teeth, may play a part in the causation.

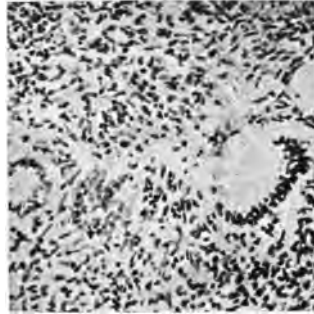


Fig. 262.—Tubercle of the tongue (Karg and Schmorl).



Fig. 263.—Actinomycosis of the cheek (Illich).

Lupus of the face may extend to the mouth. It is distinguished by the associated cicatrization. Secondary carcinomatous change may occur in the base of the lesion (lupus carcinoma).

Syphilis is most frequently secondary, occurring in the form of

mucous patches upon the lips or tongue, or as more elevated condylomata, which in healing cause irregular contractions or whitish or opaline thickenings of the mucous membrane. A simple syphilitic catarrhal angina may occur. Gummatous infiltrations may appear in a localized form or as irregular involvements. On the dorsum of the tongue, their commonest seat in this organ, they produce deep, ragged excavations. They are usually deep seated and, on healing, fissuration and deformity may result. The tongue is the most frequent seat. The primary syphilitic lesion (chancre) resulting from direct inoculation is occasionally observed upon the lips, tongue, or pharynx.

Actinomycosis affects the tongue, gums, and jaw-bone, and is characterized by a slowly infiltrating process with a tendency to necrosis and suppuration, in which the alveolar processes of the jaw-bone are generally attacked. The lesion in the mouth may be insignificant, while the secondary involvement of the cheeks or of the lymphatic glands below the jaw and in the neck may be extensive (Fig. 263).

Leukemic Stomatitis.—In acute leukemia ulcers of the mouth are frequent at the onset and throughout the disease. The gums may present an ulcerated appearance resembling that seen in scurvy. Considerable necrosis and hemorrhagic infiltration are common. Nodular infiltration of the adenoid tissues at the base of the tongue and in the pharynx also occur in acute leukemia, but more commonly in the chronic form.

TUMORS

Papillomatous growths of the mucous membrane are occasionally observed. *Fibroma*, *lipoma*, *myxoma*, and even *chondroma* are rare forms of tumors of the submucous tissue of the tongue or other parts of the mouth. Not rarely they are congenital. *Lymphadenoma* or *lymphosarcoma* may occur at the root of the tongue, where it takes origin from the lymphatic follicles or the lingual tonsil. *Sarcoma* of other parts of the mouth is rare, excepting as an extension from sarcoma of the jaw-bone and other parts.

Epithelioma or *carcinoma* is the most important new growth of the mouth, and in nearly all cases is of the squamous-celled variety. The favorite seats are the lower lip, usually toward one side of the mouth, and the tongue. It appears as an irregular nodular elevation which tends to ulcerate upon the surface and spread to adjacent structures. Metastasis usually occurs to the submaxillary and cervical lymphatic glands.

The name "epulis" is a clinical term applied to tumors arising from the alveolar process. Sarcoma and endothelioma are the commonest forms.

Nodular masses having the structure of the normal thyroid gland have been found at the base of the tongue.

Cystic formations, due to agglutination of the mouths of the mucous glands, are met with upon the tongue and lips.

Cysts are especially frequent beneath the tongue, at the sides of the

frenum. These have been termed *ranula*, and are formed by the dilatation of the ducts of the small mucous glands. At times ranula may be a cystic dilatation of a duct of the sublingual salivary gland or that of a submaxillary gland. Ranula is usually found as a rounded or elliptical tumor which may fill the floor of the mouth and displace the tongue backward and upward. The contents consist of somewhat gelatinous albuminous liquid. They may be due to stenosis of the excretory duct by inflammation or blocking by a stone. Cysts may arise at the base of the tongue from the remains of the thyroglossal duct.

Hemangioma, both of the teleangiectatic and cavernous varieties, is occasionally seen, but a more important tumor is *lymphangioma*, affecting the tongue and lips and giving rise to the conditions known as macroglossia and macrocheilia. In these conditions there is a uniform enlargement of the tongue or lips, and on section distended lymphatic spaces more or less filled with liquid and round cells are detected. Such enlargements are usually congenital, and are especially met with in cretins.

Angiomata of sarcomatous or carcinomatous nature have been seen in the tongue.

THE TEETH

Anomalous Development.—Unnatural largeness or, on the contrary, lack of development is frequently observed. Complete absence of the teeth has been noted. Numerical increase or decrease is frequent. Delay in the eruption of the teeth and irregularity in their formation occur in rachitis; and a form of maldevelopment of the upper central incisor teeth of the permanent set is observed in cases of congenital syphilis (*Hutchinson's teeth*). The characteristics of this condition are the wedge shape of the teeth, the cutting-edge being smaller than the crown, and the concave notching of the cutting-edge (see Fig. 119). Hutchinson's teeth are not entirely peculiar to congenital syphilis, being sometimes seen in rachitis.

Caries of the teeth results from malnutrition, digestive disturbances, and lack of cleanliness. Micro-organisms which lead to acid fermentation contribute to the causation by forming acids which dissolve calcium salts, soften the enamel, and occasion fissures through which other bacteria (bacilli and micrococci) may gain entrance into the channels of the dentin. The soft teeth of pregnant women are due to the reduction of calcium which is being given to the fetus.

The carious process consists in a gradual disintegration of the enamel and dentin, with the formation of more or less granular detritus in which bacteria are abundant. The process may penetrate to the pulp of the teeth and set up a secondary inflammation, or pulpitis.

Inflammation of the pulp of the teeth may occur in association with caries, or sometimes independently. The pulp becomes reddened and swollen, and may present hemorrhages and, later, suppuration. The inflammatory process tends to spread through the roots of the teeth to the tissues surrounding the roots and to the alveolar periost-

teum. Abscesses may thus be formed about the teeth, and may spread to the tissue of the gums (*alveolar abscesses*), eventually rupturing upon the surface.

Tumors composed of tissue resembling the normal dentin are spoken of as *odontomata*, and may be solid or cystic. They arise from the pulp during the process of development and form irregular outgrowths of the crown or roots. Similar outgrowths, resembling the enamel or dentin, or cement substance, are more frequent in later life, and have been designated as *odontinoids*.

Sarcomata and *fibromata* may spring from the pulp during the development of teeth or from the connective tissue about the roots; and *polypoid outgrowths* (hypertrophied granulations) from the pulp may be met with in association with caries of the teeth and pulpitis.

The most important tumor is the *giant-celled sarcoma* of the alveolar process of the jaw. This is known by the name of "epulis," though, strictly speaking, the term is applied rather to the situation than to the kind of tumor. Extensive enlargements of the jaw-bone and destruction of the surrounding tissues may ensue.

Cysts are met with in the alveolar processes, and arise from the primary follicles in which the teeth are developed. These may contain epithelium and teeth. There are also cystic tumors of the teeth-sockets from the periosteum of the jaw-bone.

THE PHARYNX AND TONSILS

CIRCULATORY DISTURBANCES

Anemia of the soft palate and other portions of the pharynx occurs in general anemia and in cases of phthisis or other wasting diseases. The mucous membrane may be decidedly pallid.

Active hyperemia or congestion occurs in the beginning states of inflammation and when irritants have been in direct contact with the mucous membranes.

Passive hyperemia is seen in heart disease, emphysema, phthisis, and other chronic pulmonary affections. In these cases the mucous membrane is dark red, and not rarely becomes somewhat edematous.

Edema of the pharyngeal tissues is found in association with inflammatory affections, and may occasion considerable stenosis.

Hemorrhages may be the result of direct injury, as in the swallowing of fish-bones and the like, or may occur in the form of petechiæ in purpura and other hemorrhagic diseases and in intense infections (small-pox, septicemia).

INFLAMMATIONS

Catarrhal pharyngitis, or **angina**, may affect the entire lining membrane of the pharynx, or may be limited to the tonsils or other parts. It results from direct irritation by hot liquids or chemical substances, from exposure to cold, and particularly from infections. Angina, or

sore throat, is met with in many of the infectious fevers, or may appear as an independent infection.

The mucous membrane presents a bright-red color, is somewhat swollen, and covered with tenacious exudation composed of mucus and desquamated cells. Small vesicular elevations may form, and after the rupture of these, erosions or even superficial ulcers are sometimes seen. Occasionally there are hemorrhagic extravasations.

A form of catarrhal pharyngitis, known as *herpetic angina*, is analogous to herpes of the skin, and may accompany facial or labial herpes.

Chronic catarrhal pharyngitis is met with in persons who use the voice excessively, especially in the open air. It may also result from the abuse of tobacco or alcohol. The posterior wall of the pharynx and the pillars of the soft palate are particularly involved. The mucous membrane is swollen in the earlier stages, but later becomes atrophic, and is marked by slight granular elevations, which are either hyperplastic lymph-follicles or distended mucous glands. The veins in the submucous tissue are enlarged, and are visible through the atrophic mucous membrane as tortuous channels. Chronic hyperplasia of the tonsils and chronic laryngitis are frequently associated.

Phlegmonous pharyngitis may result from wounds of the pharynx, or may be associated with intense infections, such as pseudomembranous tonsillitis and pharyngitis, particularly the forms due to streptococci. It may result from pustular pharyngitis in small-pox, or from glanders of the pharynx. Phlegmonous tonsillitis sometimes extends to the peritonsillar tissues as far as the retropharyngeal wall.

The soft palate, uvula, arches, or other parts affected are swollen and tensely distended. There may be congestion or deep cyanosis and edematous exudation. The usual termination is suppuration, but sometimes gangrenous necrosis ensues. General septicemia is frequently the result.

Retropharyngeal Abscess.—This condition may occur secondarily after traumatic or infectious pharyngitis as above described. Phlegmonous pharyngitis primarily affecting the retropharyngeal tissues may be due to caries of the cervical vertebræ; occasionally it occurs in the infectious fevers in consequence of embolism, or infection of the deep-seated lymphoid nodes of the pharynx.

Pseudomembranous pharyngitis may be caused by the *Mycobacterium diphtheriæ*, in which case the disease is diphtheria, or it may be due to a variety of other micro-organisms, or to irritating gases, steam, and like causes. Non-diphtheritic pseudomembranous pharyngitis is especially common as a complication of scarlatina, measles, and other infectious diseases, and seems in these cases to be caused by the *Streptococcus pyogenes*. The appearance of the throat may be identical with that observed in diphtheria, but extensive necrosis is more common, while typical pseudomembranes are less frequent.

The mucous membrane and the underlying parts, especially the tonsils, become greatly swollen and edematous, and subsequently suffer necrotic changes.

There is formed upon the surface of the throat a whitish or yellowish patch, or several patches, which tend to coalesce and extend from the region of the tonsils to the pillars of the fauces and the uvula, or to the mouth, nose, or larynx. The pseudomembrane is quite firmly attached to the mucous membrane, and cannot be removed without tearing away part of the underlying tissues. Microscopically, the deposit is found to consist of granular or fibrillar fibrin entangling more or less degenerated leukocytes and epithelial cells. In the deeper layers intense congestion and round-cell infiltration are observed; in the superficial strata degenerated cells and detritus, together with masses of bacteria, are conspicuous.

The neighboring lymphatic glands, notably those below the angle of the jaw, enlarge and may suppurate, and sometimes extensive cellulitis and suppuration of the floor of the mouth (Ludwig's angina) occur. There are intense systemic intoxication and infection, and secondary lesions are frequently developed in various organs (nephritis, myocarditis, etc.). The non-diphtheritic forms of pseudomembranous pharyngitis may be distinguished from the diphtheritic forms, in typical cases, by the greater intensity of the local (necrotic) processes, the earlier and more marked involvement of the local lymphatic glands, and by the greater tendency to nephritis; but, unfortunately, atypical cases are very common, and an absolute diagnosis can be made by bacteriological study alone.

Tonsillitis may be a part of a general pharyngitis, or it may occur as an independent affection. Several varieties are described.

Catarrhal tonsillitis results from the same causes as catarrhal pharyngitis in general, and presents similar appearances. The tonsils are usually somewhat enlarged.

Lacunar or follicular tonsillitis occurs from similar causes, and may involve the normal tonsil or one affected by chronic hypertrophy.

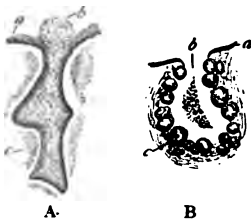


Fig. 264.—Crypts in cases of tonsillitis: A, Acute lacunar; B, chronic hypertrophic: a, surface epithelium; b, accumulated contents of crypt; c, lymphoid follicles surrounding crypt (Kaufmann).

The surface of the tonsil is marked with small white or yellowish spots, into which the end of a probe may be inserted. These are the lacunæ or crypts distended with masses of epithelial cells more or less degenerated. Bacteria of various kinds may be found in the contents of the lacunæ, and doubtless play an important part in the etiology. Staphylococci, streptococci, pneumococci, tubercle bacilli, and the bacillus of diphtheria have all been observed. The latter two forms may be present merely as accidental associations, but may possibly play an etiological part. Ulceration may occur in the

walls of the lacunæ, and the surface of the tonsil may be considerably broken down. In other cases the bacteria may penetrate the tonsil at the bottom of the lacunæ, and *phlegmonous tonsillitis*, or *quinsy*, may result (see below). The contents of the lacunæ may be

discharged upon the surface, and may adhere for a time as a yellowish-white caseous pellicle, resembling diphtheritic pseudomembranes in appearance. In other cases the contents of the crypts are retained, undergo inspissation, and may even calcify. A certain amount of catarrhal pharyngitis may be associated, but the follicular ulcers are rarely seen beyond the tonsils.

Phlegmonous tonsillitis, abscess of the tonsil, or quinsy, may be the result of simple catarrhal or of follicular tonsillitis, or may be associated with phlegmonous inflammation of other parts of the pharynx. One or both of the tonsils may be affected. Redness and swelling are noted in the earlier stages, but later the mucous membrane is pallid or even yellowish. Microscopically, diffuse round-cell infiltration and eventually focal collections leading to abscess formation are detected. The peritonsillar tissues may be involved, and spreading phlegmonous inflammation results. Rupture may take place into the pharynx, or the ulceration may extend outward, causing discharge upon the neck at the angle of the jaw. The internal carotid artery may be perforated.

Enlargement of the submaxillary and cervical lymphatic glands is commonly observed. General septicemia of mild type is not infrequent; myocarditis, endocarditis, and nephritis may result. The association of tonsillitis and rheumatism has occasioned much discussion. It is very probable that rheumatism frequently follows tonsillitis, the latter being the first effect of micro-organismal invasion, which eventually causes rheumatism.

Chronic tonsillar hypertrophy may result from repeated attacks of simple catarrhal or of follicular tonsillitis. The lymphatic constitution or status lymphaticus is a factor of importance. The tonsils are enlarged, usually irregularly so, and are harder than normal. On section the connective-tissue reticulum and septa are found increased, and the lymphoid follicles are likewise hyperplastic. Pressure upon the orifices of the lacunæ not rarely causes obstruction and repeated attacks of lacunar tonsillitis. Retention and calcification of the contents of the crypts are particularly common in the lacunar tonsillitis of hypertrophic tonsils. Chronic hypertrophy of the tonsils very often occurs in rachitic or badly nourished children in association with hyperplasia of the lingual tonsil and nasopharyngeal adenoid tissues—the clinical *adenoids*. Distinct evidences of inflammation are wanting in such cases, and the condition seems rather a form of simple hyperplasia of the lymphoid structures.

Pathological Physiology.—Acute tonsillitis may occasion only local symptoms, such as pain, difficulty in swallowing, etc., but in many cases there are general symptoms—fever, disturbances of appetite, etc. The latter vary in severity according to the particular infectious cause of the disease.

A chronically enlarged tonsil probably always contains bacteria, and this may constitute a focal infection, whence bacteria may be liberated to cause damage elsewhere. The streptococci of the tonsils have been suspected of responsibility for chorea, arthritis deformans, and

other subacute infections. Chronically diseased tonsils have been found to contain a toxic substance, which when absorbed excites antibodies like a parenterally introduced protein, and acts as a protoplasm poison. The glands containing streptococci seem to contain most of this poison. This may aid in the production of the above diseases.

PRESSURE NECROSIS

This condition occurs upon the anterior and posterior walls of the pharynx, opposite the cricoid cartilage. It is met with in marantic persons occupying a dorsal decubitus, and is caused by the backward pressure of the cricoid cartilage against the opposite vertebra. The mucosa becomes necrotic, and more or less extensive ulcerations are formed. Complete perforation of the pharyngeal wall sometimes occurs.

INFECTIOUS DISEASES

Diphtheria of the pharynx usually begins in the mucous membrane covering the tonsils, and spreads to the pillars of the fauces, to the uvula, the posterior wall of the pharynx, the cheeks and tongue, the posterior nares, or to the larynx. It rarely invades the esophagus, but may sometimes extend along this structure as far as the stomach.

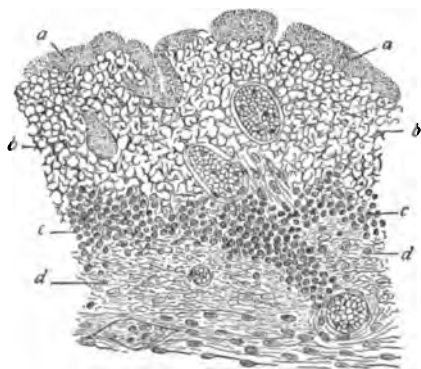


Fig. 265.—Pseudomembranous inflammation of the uvula: a, a, masses of micrococci; b, b, necrotic cells; c, c, round-cell infiltration; d, d, fibrin network (Ziegler).

The specific cause is the *Mycobacterium diphtheriæ* (see Diphtheria, p. 285). The characteristic lesion is a pseudomembrane, which is formed on the surface and within the mucous membrane. This first appears as a grayish or yellowish-white pellicle, more or less firmly attached to the mucosa; it spreads rapidly, and may cover the whole of the pharynx in a day or two. In other cases the disease progresses slowly or remains quite limited. The underlying tissues become swollen by inflammatory infiltration (cellular and edematous), and swallowing and breathing

may then be greatly obstructed. When the pseudomembrane is removed from the surface a raw and more or less necrotic base is exposed. Microscopically, the surface of the pseudomembrane is found to consist of a mass of debris, often containing micrococci and other bacteria, as well as the specific organisms, in great numbers. Somewhat more deeply the membrane is composed of a fibrinous reticulum or masses of fibrin entangling degenerated epithelial cells and leukocytes. Still more deeply the tissues of the pharynx are found intensely

congested and infiltrated with round cells (Fig. 265). In the late stages of the disease extensive necrosis of the mucosa and submucosa may occur.

In some cases diphtheria may undoubtedly present the lesions of an ordinary lacunar tonsillitis, and the clinician may be unable to determine the nature of the disease.

Associated Conditions.—Some enlargement of the lymphatic glands at the angle of the jaw is usual, and exceptionally this may terminate in suppuration. Lesions of the internal organs, especially the heart and kidneys, are not infrequent, and disease of the peripheral nerves is a common sequel (see Diphtheria, p. 287).

Vincent's angina is a mildly infectious disease characterized by superficial ulceration upon which a lightly adherent pseudomembrane lies. The process usually begins upon or near the tonsils and spreads slowly; it is a superficial ulceration of the epithelium, while in the corium there is a moderate round-cell infiltration. The fusiform bacilli, and the spirilla probably growing from them, are found in the membrane and on the base of the ulceration (see page 340).

Pharyngomycosis Leptothricia.—This condition is met with on the tonsils; and less frequently the pillars of the fauces, uvula, and other parts of the pharynx. It occurs in persons of lowered vitality, and seems to be caused by the *Leptothrix buccalis*, a form of bacterium very commonly met with in the collections around the necks of the teeth. The lesions present themselves as milky-white and somewhat chalk-like outgrowths arising from the tonsillar crypts and the mucous glands. These are often tightly adherent, but occasion very little inflammation of the surrounding tissues. Microscopically, the thread-like parasite is found in abundance.

Tuberculosis may occur in the pharynx in the form of subepithelial tubercles, which break down and occasion more or less extensive ulcerations.

Tuberculosis of the tonsils may be primary or secondary. In the former case infection probably occurs from the invasion of the crypts by tubercle bacilli; this condition is doubtless more common than has generally been supposed. Secondary tonsillar tuberculosis usually follows tuberculosis of the lungs or larynx. In either case there are formed in the tonsils small tubercles which rapidly increase in size, fuse, and subsequently undergo caseous change. Discharge of the caseous matter upon the mucous surface is not unusual, and occasions ulcer-like formations. Secondary infection of the cervical and submaxillary lymphatic glands is not infrequent.

Syphilis may occur in the pharynx in the form of the primary lesion or chancre, as simple catarrhal angina, as mucous patches, or as gummata. The last are prone to undergo ulceration with secondary cicatrization. Extensive distortion of the pharyngeal structures may be the result of the scar formation.

Glanders and lepra sometimes invade the pharynx.

Typhoid ulcers are occasionally met with.

TUMORS

Among the tumors of the pharynx, fibroma, lipoma, and papilloma are occasionally found on the soft palate, uvula, or tonsils. Of the malignant tumors, sarcoma of the tonsils is most important. It is usually of the lymphosarcomatous variety, and is rapid in growth and highly destructive. Epithelioma may occur at the base of the tongue, in the soft palate, or tonsils. Other varieties of cancer are rare.

Polypoid tumors of the nasopharynx and hyperplastic adenoid growths of the same situation frequently extend downward into the pharynx proper.

THE SALIVARY GLANDS

Inflammation of the salivary glands affects the parotid most frequently.

Parotitis may be the expression of an independent infection (mumps); or may be secondary to various infectious diseases, such as typhoid fever; typhus fever, or pyemia. Parotitis sometimes occurs in association with diseases or injuries of the abdomen or pelvic organs. A reflex or "sympathetic" inflammation has been assumed as the cause of the parotid disease by some, but recent investigation seems to indicate that in all cases the real cause is infection through the duct.

The specific cause of mumps has not been isolated (see page 354). The infection probably occurs through the parotid duct, and in some instances inflammations of the mucous membrane of this duct have been found to precede the parotitis. The gland is swollen and tensely distends its capsule. The inflammatory exudate is probably largely serous, as it may be absorbed and removed in the course of a very short time. The disease scarcely ever terminates in suppuration. Orchitis is an occasional complication, and may be followed by atrophy of the testes.

The secondary parotitis occurring in the course of various infectious diseases is characterized by a marked tendency to abscess formation, and at all stages of the affection round-cell infiltration is conspicuous. After the formation of an abscess perforation may take place upon the cheek or into the mouth, and sometimes salivary fistulæ (see below) are established. Chronic induration of the gland may remain after attacks of inflammation. Chronic parotitis may also result from certain intoxications (lead, mercury, iodid of potash) or may occur in chronic nephritis or syphilis. Mikulicz described a form of simultaneous enlargement of the parotid, submaxillary, and lachrymal glands. The etiology is unknown.

The submaxillary gland is occasionally affected with the parotid, or independently, in mumps. The sublingual gland rarely becomes inflamed.

Angina Ludovici, or **Ludwig's angina**, is a septic inflammation of the tissues of the floor of the mouth surrounding the submaxillary gland. It may result from carious processes at the roots of the teeth,

or from infection of the submaxillary lymphatic glands in the course of various infectious diseases, particularly scarlet fever. The most frequent termination is abscess formation, with perforation externally or into the mouth. Occasionally rapid necrosis or gangrene results. Many different organisms have been found, but to none is ascribed any specific importance. The characteristic of this affection is the density of the infiltration, there being almost a wooden hardness. The parts are dark red.

Tumors.—The parotid gland is more frequently the seat of tumors than the other salivary glands. Benign tumors, such as fibroma, lipoma, or chondroma, are rare. The most common new growth is the so-called “mixed tumor,” which is essentially sarcomatous, with the addition of fibroma, chondroma, or myxoma, and at times of all these. Some of the mixed tumors are said to be endotheliomata, but the decision is difficult because of the atypical growth of the glandular acini. Adenoma and carcinoma are occasionally primary.

Diseases of the Salivary Ducts.—*Salivary fistulae* may result from traumatic injuries or from the perforation of abscesses. They most frequently affect the duct of the parotid.

Concretions composed of phosphate and carbonate of calcium are occasionally observed, and may lead to obstruction of the ducts.

Cystic dilatation of Steno’s or Wharton’s duct, or of those of the sublingual glands, may be due to concretions or to inflammatory processes at the mouths of the ducts. Oval or elliptical tumors are formed, and contain transparent, viscid liquid. Such cysts belong to the group of conditions designated as *ranula*, but more frequently this is due to obstruction of the small mucous glands beneath the tongue.

THE ESOPHAGUS

CONGENITAL DEFECTS

Occasionally the esophagus is double, being divided into two parts by a septum. Complete absence of the esophagus may occur in certain monstrosities; more frequently there is partial absence of the lumen about the middle of the tube. The lower end of the esophagus in such cases communicates with the trachea, while the upper end terminates as a blind pouch. The intermediate defective portion may be represented by a fibromuscular cord, or may be entirely wanting. Fistulous communications may pass from the side of the neck to the upper end of the esophagus or pharynx. They are due to incomplete closure of the branchial clefts.

CIRCULATORY DISTURBANCES

Anemia may be due to general anemia; **active hyperemia**, to the irritation of hot liquids or chemicals.

Passive congestion results from diseases of the heart or lungs, or from portal cirrhosis of the liver. In the latter condition large *varicosi-*

ties may be established in the lower end of the esophagus, due to the communications between the left coronary vein of the stomach, the esophageal veins, and vena azygos. Hemorrhage may occur from these dilated veins, as they lie close beneath the mucous surface.

INFLAMMATIONS

Catarrhal esophagitis is characterized by hyperemia and desquamation of epithelium, with very little liquid secretion. It may be due to the ingestion of irritating acid or alkaline liquids, to scalding, or occasionally to direct traumatic irritation. Superficial erosions are sometimes met with.

Chronic catarrhal esophagitis is found in cases of passive congestion continued for a long time, and particularly in alcoholics. The mucous membrane is thickened and irregularly pigmented. Occasionally erosions are met with, and more commonly areas of hypertrophy of the mucosa.

Pseudomembranous esophagitis may result from extension of pharyngeal diphtheria or pseudomembranous pharyngitis, or it may be primary in rare instances.

Ulcerative esophagitis may occur as the result of pustular eruption in small-pox, or in consequence of irritation of foreign bodies. It is not unusual to find small or even large ulcers in the mucosa of esophageal diverticula. These are occasioned by the retention of food. Peptic ulcers similar to those occurring in the stomach are occasionally found in the lower end of the esophagus.

Phlegmonous esophagitis is rare. It may result from the extension of intense inflammation of the mucous membrane into the submucous tissue, or to penetration of the mucosa by sharp points of fish-bones and the like.

The inflammation arising after swallowing corrosive or irritant substances may partake of all the above forms. It is usually, with milder substances, a desquamative process, but these may penetrate and produce a pseudomembranous condition due to destruction and separation of the mucosa. With the more corrosive agents a rapid necrosis of mucosa or even submucosa may occur, with later development of hemorrhages or dry ulcers. Suppuration, diffuse or localized, may occur. Connective-tissue overgrowth leads to alterations in the lumen. After severe damage the whole thickness of the mucosa may not be restored, there being merely a coating of epithelium for the scar tissue.

STENOSIS

Stenosis of the esophagus may be due to the pressure of tumors or aneurysms upon the esophagus, to the lodgment of foreign bodies, to the growth of tumors in the esophageal walls, or to stricture of the esophagus. The last most frequently results from the healing of ulcerations caused by the swallowing of corrosive liquids. Syphilitic and

posttyphoidal strictures are rare. Carcinoma of the esophagus may obstruct by the growth within or by the attendant contraction of the walls. Occasionally stenosis by malformation is congenital.

Acute stenosis is a muscular spasm of the walls due to irritation, or as a part of hysteria or general convulsions.

DILATATION

Dilatation of the esophagus may occur in the form of a *simple dilatation* or ectasia, or in the form of *diverticula*. The former variety is common at the lower end of the esophagus, and is occasioned by obstructions at the cardiac end of the stomach, or at the point where the esophagus passes through the diaphragm. The dilatation may reach considerable size. The mucous membrane is usually thin and often ulcerated.

An "idiopathic form" has been described, in which there is more or less uniform or spindle-shaped widening, probably due to atony of the musculature or to vagus disease. Spasmodic contraction of the cardia is also described as a cause.

Diverticula may be of two kinds, those due to pressure from within (*pulsion diverticula*) and those due to traction from without (*traction diverticula*) (Fig. 266). The former are more commonly found in the upper portion of the esophagus or the lower part of the pharynx, and arise from the posterior wall of the esophagus. They are due to thinning of the muscular coat and to hernia-like protrusion of the mucous membrane. They may reach considerable size by gradual distention. The traction diverticula are most frequently found near the lower end, opposite the bifurcation of the trachea. They are caused by adhesion of diseased bronchial glands and subsequent contraction of the attachments. They occupy the anterior wall of the esophagus and have a somewhat funnel shape. Perforation may occur, with the development of septic infection of the pleura, pericardium, or lungs. Perforation of the pulmonary arteries may lead to fatal hemorrhage.



Fig. 266.—Traction diverticulum of the esophagus (modified from Birch-Hirschfeld).

PERFORATION AND RUPTURE

The esophagus may be perforated by necrotic or suppurative processes surrounding it, or as the result of ulcers proceeding from within. Aneurysms of the thoracic aorta occasionally rupture into the esophagus. Retropharyngeal abscesses and phlegmonous inflammations of the deep cervical tissues may likewise discharge into the esophagus. Per-

foration by ulcers beginning within may be due to the lodgment of foreign bodies, or to the pressure of the cricoid cartilage in cases of great asthenia (see Pharynx). Perforation of the lower end of the esophagus may result from peptic ulcers or *esophagomalacia* due to regurgitation of gastric liquid either before or after death. Spontaneous rupture of the esophagus occasionally takes place. In these cases there is doubtless always some antecedent weakness of the walls.



Fig. 267.—Carcinoma of upper end of esophagus (from a specimen in the collection of Dr. A. J. Smith).

INFECTIOUS DISEASES

Tuberculosis of the esophagus is extremely rare, and most frequently results from extension of tuberculous adenitis of the bronchial glands.

Syphilis occasionally occurs in the form of ulceration and cicatrization, leading to stenosis.

Typhoid ulceration is probably more frequent than has been generally thought. Occasionally stenosis is caused by the cicatrices of the healed ulcers.

Thrush may extend from the mucous membrane of the mouth and pharynx.

Foreign bodies, like small bones, have been found embedded in the esophageal wall.

TUMORS

Fibroma, *myoma*, *lipoma*, or even *sarcoma* may occur as somewhat polypoid submucous tumors, but are rare. *Papillomata*, in the form of outgrowths of the mucous membrane, are more common.

The most important tumor is *carcinoma*, which is usually found in the lower part, generally at the position where the left bronchus crosses the esophagus, or near the passage of the tube through the diaphragm. It may, however, be found at any part. The squamous variety is the most common, though a few instances of glandular carcinoma are recorded. The tumor usually involves the entire lumen of the esophagus, projecting inward and forming irregular elevations of the mucous membrane. Later, the growth extends outward through the muscular coat to the fibrous outer layer, and even to the surrounding tissues. Dilatation occurs above the tumor, and occasionally perforation results from ulcerations caused by retained food. Local or more distant metastasis may take place.

Cysts of the esophagus may occur. They are supposed to be due to misplaced lung or tracheal tissue. Many of them contain ciliated epithelial lining, strongly suggesting the latter origin.

THE STOMACH

CONGENITAL DEFECTS

Complete absence of the stomach has been found in certain monstrosities; but stenosis or atresia of the pylorus, division by the formation of septa, and hour-glass contractions have been more frequently observed. In cases of transposition of the viscera the stomach may be reversed in its position, the pylorus being on the left side, the cardiac end to the right.

Congenital hypertrophic stenosis of the pylorus with or without dilatation of the stomach has been found more common than previously thought. The hypertrophy may affect either the pyloric mucosa or muscularis, or both. This is entirely apart from spastic stenosis of the pylorus in children, which has no anatomical basis. There may be some inflammation with the pyloric stenosis.

There is occasionally a hypertrophy of the middle of the stomach wall which gives a picture somewhat like hour-glass stomach, and, of course, this condition can be simulated in later life by cicatricial contraction. During digestion the midpiece of the organ contracts so far that there is a similarity to congenital hour-glass deformity.

CIRCULATORY DISTURBANCES

Anemia of the mucous membrane is found in cases of general anemia, particularly in pernicious anemia. The mucosa has an extremely pallid appearance, and is prone to undergo fatty degeneration and atrophy.

Hyperemia.—*Active congestion* occurs in the beginning stages of inflammation of the mucous membrane of the stomach, and results from irritating mechanical or chemical agents. The mucosa is bright red in color and may present minute hemorrhages. Moderate hyperemia is functional during the period of digestion.

Passive hyperemia occurs as a result of obstructive heart disease or, more particularly, from obstruction of the portal circulation by cirrhosis or other diseases of the liver. Pulmonary affections, by interfering with the outflow of blood from the right side of the heart, may also occasion congestion of the stomach. The mucosa is dark red in color, swollen, and often edematous. Minute hemorrhages may occur, and small erosions may appear upon the surface. The changes are more marked near the pyloric end of the stomach. When the congestion has persisted for some time, dark reddish or bluish pigmentation, usually occurring in punctate form, is developed and chronic gastritis results.

Hemorrhage in the mucous membrane or from the mucous membrane of the stomach results from a variety of causes. Small petechiæ are met with in active or passive congestion and in acute inflammations, and they may follow thrombosis or embolism of the gastric vessels. Milder poisons cause them. They are also present in various infectious

or hemorrhagic diseases, such as purpura, scurvy, septicemia and the like, and in anemic affections like pernicious anemia. In many cases punctiform hemorrhages are developed just before death.

These are all submucous hemorrhages, from the overlying mucosa of which the gastric juice may digest the covering, leaving erosions which may go on into distinct ulcerations.

Larger hemorrhages, and particularly hemorrhages into the cavity of the stomach, result from intense passive congestion in cardiac disease or cirrhosis of the liver, and from gastric ulceration or carcinoma. When large vessels have not been eroded the blood escapes gradually, and may be vomited in a semidigested and disorganized condition (coffee-ground vomit). This is peculiarly significant of carcinoma. When one of the larger vessels has been eroded, large quantities of fresh blood may be vomited and rapid death may occur. Occasionally hemorrhage from the stomach in considerable quantity occurs in cases in which there is no visible lesion of the mucosa.

Melena neonatorum, the vomiting of blood by the newborn, results from gastric hemorrhage due to disturbances of circulation because of insufficient respiration, and possibly in other cases is a variety of infectious hemorrhagic disease.

INFLAMMATION

Acute inflammation of the mucosa, or acute gastritis, results from irritation by chemical, mechanical, or thermal agents. Some cases are doubtless due to infection. The mucous membrane is bright red and covered with more or less viscid mucous exudate. Punctate hemorrhages may occur. Microscopically, there are found: marked mucous degeneration of the cylindrical cells of the tubules, and desquamation and granular degeneration of the cuboidal cells in the fundus of the glands. The mucous membrane between the tubules is infiltrated with round cells, and not rarely the same process occurs in the submucosa. The collections of lymphatic tissue (follicles) in the mucous membrane are often hyperplastic. Acute gastritis is more frequently found near the pyloric end than elsewhere.

In considering the rôle of bacteria in the causation of gastritis it must be remembered that the bacteria normal to the stomach are few and not pathogenic. Most pathogenic bacteria are destroyed in the normal stomach. When, however, gastric mucosa and juice are altered by irritant poisons or by the fermentations and putrefactions arising in food taken to excess, especially in the presence of deficient propelling power by the muscular coat, the natural protective powers of the stomach are reduced. In such cases pathogenic germs introduced with the food thrive and attack the damaged walls. The normal flora comprises *sarcinæ*, moulds, and yeasts.

Pseudomembranous gastritis may result from the ingestion of corrosive poisons, and is occasionally seen in small-pox, typhus fever, and various forms of septicemia. It may be met with in diphtheria, and

may be due to direct extension of the process along the esophagus. The surface of the mucosa is covered with an irregular membrane, and necrosis and ulceration are not rarely observed, especially in cases due to corrosive poisons.

Ulcerative Gastritis.—Small erosions may be found in cases of extreme congestion or petechial hemorrhage, as well as in acute gastritis. Actual ulceration is seen in pseudomembranous gastritis, and occasionally as a result of septic embolism in the mucosa in cases of malignant endocarditis. Infectious ulcerations occur in gastro-intestinal tuberculosis, anthrax, and in typhoid fever, but are very rare.

Chronic gastritis may result from repeated attacks of acute gastritis, and is especially prone to occur from improper habits of eating or from the abuse of alcohol. Chronic congestion, such as occurs in heart disease, strongly predisposes.



Fig. 268.—Chronic gastritis, showing polypoid projections of the mucosa.

Pathological Anatomy.—The appearance of the mucous membrane varies greatly. In the milder cases the surface is more or less irregular and granular, and is covered with mucous exudate. The color may be grayish, but in cases in which passive congestion has preceded the development of gastritis it is often slate colored from pigmentation.

Microscopically, there may be found mucous degeneration of the cylindrical epithelium of the tubules, and desquamation and not rarely proliferation of the secretory epithelium in the fundus of the glands. The glands may be considerably dilated and filled with mucous exudate and desquamated cells. The interglandular tissues are infiltrated, and may be thickened by the formation of new connective tissue; the same process may involve the submucous coat. The blood-vessels of the latter are often greatly dilated and their walls may be thickened. In the later stages the glands may undergo progressive atrophy, the epithelium disappearing almost entirely and the lumen of the gland be-

coming less and less distinct. Coincidentally with these changes, and to some extent causing them, there is fibrous overgrowth of the interglandular tissues.

In some instances the contraction of the new-formed connective tissue causes protrusions of the mucous membrane or polypoid elevations (Fig. 268). These may still further enlarge by proliferation and cystic distention of their glandular elements. In other cases the proliferative changes in the interglandular tissues may be more diffuse and the mucous membrane more regularly thickened. To both of these forms the name *hypertrophic gastritis* may be applied. In still other cases the formation of fibrous tissue causes pressure-atrophy of the glands; the surface in these cases becomes smooth and the mucosa greatly thinned (*atrophic gastritis*).

The sclerotic process may involve not only the mucous membrane, but also the submucous and even the muscular coat. In such cases the thickness of the walls of the stomach may increase greatly, and the size of the organ greatly diminish by contraction. The terms *interstitial gastritis*, *linitis gastrica*, and *leather-bottle stomach* have been applied to such cases. It is sometimes difficult to distinguish such cases from diffuse scirrhus carcinoma.

Pathological Physiology in Gastritis.—All forms of gastritis cause disturbances of the functions of the stomach, designated by the terms *dyspepsia* and *indigestion*. These disturbances are due to abnormal secretion of the gastric glands, reduced motor power of the walls of the stomach, and altered conditions of the nervous mechanism. The most important alteration of secretion is reduction of the amount of hydrochloric acid. This is almost constant in uncomplicated gastritis; in some cases there is practically no hydrochloric acid reaction. The ferments, pepsin and curdling ferment, may be produced in insufficient amount, but are very rarely absent. In cases in which certain general conditions or nervous affections coexist with moderate gastritis, excess of hydrochloric acid secretion occurs. Reduction in the amount of hydrochloric acid causes delay and inadequacy of digestion of proteins. When the acid is wholly wanting, decomposition of the proteins may occur, and sulphuretted hydrogen and other products of decomposition result. Excess of hydrochloric acid interferes with salivary digestion in the stomach, and, in consequence, fermentation of carbohydrates, with production of lactic, butyric, or acetic acid and of various gases, takes place. Such fermentation, however, is not, as a rule, observed unless the motor power of the stomach is deficient and the food is retained in the stomach beyond the usual time. It is not improbable that toxic substances are produced in some cases by protein decomposition, but accurate observations are wanting.

The motor power is usually deficient in proportion to the intensity of the gastric disease. In some cases the food is retained many hours longer than the usual periods, and fermentation and decomposition are thus greatly favored. Dilatation of the stomach may be brought about by the retention of food and the accumulation of gases of decomposition,

and the dilatation, in turn, increases the motor insufficiency of the wall.

Altered conditions of the nervous mechanism of the stomach manifest themselves in a variety of ways. Sometimes there is excessive irritability of the mucosa, causing vomiting; in other cases a feeling of heaviness or pain. Alterations of appetite and of gastric motility are other results probably brought about, in part at least, through nervous disturbances.

The general metabolism suffers profoundly in gastric disease—mainly in consequence of the insufficient food eaten or digested. Emaciation and systemic depression are the clinical consequences. It is possible that toxic substances produced in the stomach contribute to the metabolic disturbances, but this remains to be proved.

GASTRIC ULCER

Gastric, peptic, or round ulcers are roughly circular defects of the mucosa and part of the submucosa, probably due to the digestive action of the gastric juice upon a section of stomach wall previously deprived of its natural resistance. Similar lesions may occur in the upper end of the duodenum and in the lower end of the esophagus. Mayo has insisted that duodenal ulcers are much more frequent than has been heretofore believed, and that they are more common in men than in women.

Etiology.—Many cases occur in young women suffering from chlorosis or anemia and general malnutrition, but the majority of peptic ulcers occur in males. The pathogenesis of these ulcers has occasioned much dispute. It is admitted that they are due to the action of the gastric juice upon parts of lowered vitality, and the term *ulcus ex digestione* is, therefore, appropriate. Increased acidity of the gastric juice is an undoubted factor. The lowered vitality which localizes the ulceration has been ascribed to many causes. Embolism or thrombosis with infarction was suggested by the shape of the ulcers, and may be the explanation for some cases. Spasm of the blood-vessels in localized areas, possibly due to stimulation of the vagus, and thickening of the walls of the vessels, leading to anemia, have been suggested, as have also direct traumatic injuries of the mucous membrane and external traumatism, causing rents of the mucous surface. Circulatory disturbances due to tight lacing are supposed by some to be important. When these peptic ulcers occur beyond the pylorus in the duodenum, they very rarely appear below where the intestinal contents are acid.

For the chronic ulcers, alterations in the position and rugosity of the mucosa probably play a part. If the mucosa be thrown or drawn mechanically into abnormal folds the circulation is naturally altered and resistance to autodigestion decreased. Adhesions without may also have such a result. By some authors blood-vessel changes are held responsible, as arteriosclerosis, endo-arteritis, and thrombosis are exceedingly common in the vessels supplying the affected parts. It is

probably well at this time, when the question is as yet unsettled, to explain peptic ulcers as the result of the action of gastric juice, probably high in acidity, upon a small locality deprived of its resistance. The multiple benign ulcers seen in general infections or blood dyscrasias are doubtless of the same origin. They seldom if ever perforate, and give no symptoms.

Gastric ulcers have been attributed to streptococcal embolism and thrombosis. Superficial ulcerations are said to occur if bile enter the stomach when there is 0.5 per cent. or more of hydrochloric acid present. Both of the above statements gain somewhat in value in view of the experimental observations that streptococci are resistant to the antibacterial action of the bile. Trypsin from the duodenal contents, entering an atonic stomach by reason of a relaxed pylorus, is said to have a potent effect on ulcer production. These observations by American workers may assist in clearing up the etiology of peptic ulcers.

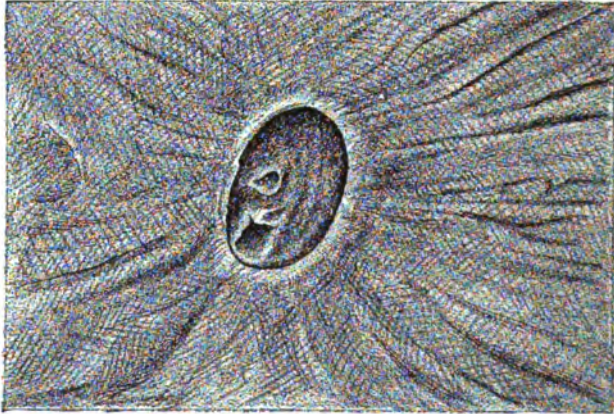


Fig. 269.—Peptic ulcer, showing erosion into a blood-vessel in the floor of the ulcer (Bollinger).

Pathological Anatomy.—Peptic ulcers are usually single, but may be multiple. They are commonly situated in the lesser curvature and the posterior wall of the stomach, near the pylorus; occasionally they are found at the fundus or at the cardiac end. A striking form is the large saddle-shaped ulcer which has a narrow part in the lesser curvature and large spreading wings in the anterior and posterior wall of the stomach. They vary in diameter from a few millimeters to 3 or 5 cm. Their shape is characteristic in that they have sloping edges, giving them a funnel form, with the apex toward the muscular coat. The shape corresponds to the distribution of the gastric arterioles. The edges may be irregular and rough, but are often, especially in older ulcers, quite smooth and rounded.

Two dangers are always imminent—hemorrhage and perforation. Constant oozing of blood may be due to erosion of the surface, and larger hemorrhages may result from ulceration of one of the larger

arterial branches of the stomach (Fig. 269). Perforation is less common than hemorrhage. When the ulcer is situated posteriorly perforation is prevented by adhesions attaching the stomach to the head of the pancreas or other structures. When the ulcer is in the anterior wall perforation is more liable to take place (Fig. 270). The rupture may occur

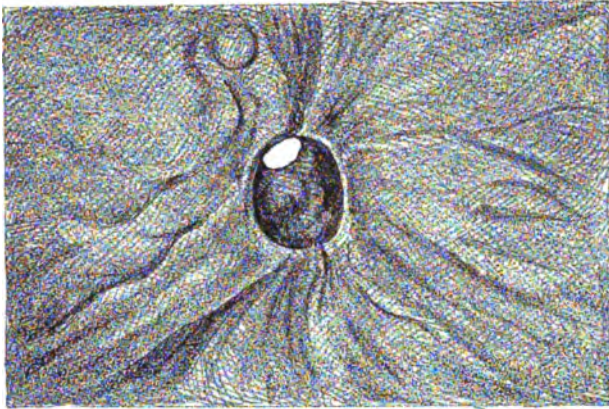


Fig. 270.—Peptic ulcer with perforation (Bollinger).

into the peritoneal cavity or into any of the surrounding structures, and fistulous communications may be established with the pleural or pericardial cavities, or even with the exterior through the abdominal walls. Abscesses of the liver, spleen, or pancreas may result from perforation into these organs.

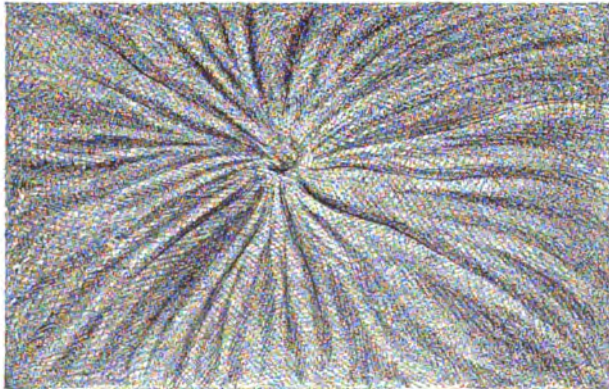


Fig. 271.—Stellate scar of a healed ulcer of the stomach (Bollinger).

Microscopically, there is little to be seen aside from loss of surface tissue. In the older cases a slight circumferential fibrous tissue increase, especially at the thickened margin, may be found.

In the healing of the ulcers scars are formed in the wall of the stomach. These have usually a rather characteristic stellate shape (Fig. 271).

In case of large ulcers extensive scars and considerable contraction of portions of the walls of the stomach result. Hour-glass contraction of the organ, or pyloric stenosis, may follow, and secondary changes, such as gastric dilatation, may ensue. Carcinomatous transformation is a not infrequent result of long-standing ulceration.

ATROPHY AND DEGENERATIONS

Atrophy of the glands or gastric tubules is frequently seen in chronic gastritis. The same condition occurs as a senile change and in association with various chronic diseases, especially pernicious anemia. A certain amount of atrophy of the entire mucous membrane results in a purely mechanical way from gastric dilatation.

Decrease in the size of the stomach as a whole may be the result of chronic gastritis, when the new-formed connective tissue contracts. In such cases the stomach may become quite small, the walls, however, increasing in thickness. Somewhat similar shrinkage in the size of the stomach occurs in some instances of infiltrating cancer of the stomach. The tumor may involve all parts of the organ equally, and cause more or less thickening of its walls, but the size of the organ is diminished by contraction of the connective tissues.

A form of true atrophy is sometimes caused by obstruction of the cardiac orifice; it is probably due, in part at least, to the insufficiency of food admitted to the stomach.

Degenerations of the mucous membrane of the stomach are met with either in association with inflammation or as independent affections.

Fatty degeneration of the epithelial cells of the glands may be the result of intoxications (phosphorus, arsenic), or of conditions such as those which lead to simple atrophy. The occurrence of atrophy and fatty degeneration of the gastric tubules in cases of pernicious anemia is of great importance, though it remains unsettled whether these conditions are the cause or result of the anemia.

Pigmentation is met with as a result of chronic congestion or hemorrhage into the mucous membrane. The mucosa has a dark red or often a slaty discoloration, which is prone to be distributed in lines or in circumscribed patches. Bluish pigmentation of the stomach sometimes occurs from the ingestion of silver.

Amyloid infiltration may be found around the blood-vessels of the submucosa, or more rarely of the mucosa itself, in cases of general amyloid disease. Amyloid ulcerations may occur.

Calcification has been met with in cases of bone disease with surcharge of the blood with earthy salts. It appears in the form of scales or plates of calcification upon the mucosa.

Gastromalacia, or simple softening of the walls of the stomach, is usually a postmortem condition, and is due to the action of the gastric juice. The nature of this process has occasioned much discussion, but it is now recognized as a postmortem condition, or as a condition occurring

during life only in the agonal period. It affects the fundus or posterior part of the stomach. The mucous membrane becomes soft and more or less gelatinous, and is grayish or yellowish in color if the mucosa was anemic, or brownish in cases in which there was congestion before death. Rupture and discharge of the contents of the stomach into the peritoneal cavity, spleen, or other adjacent organs may occur. The walls of the stomach in the affected area show granular degeneration of the component cells, but no evidences of inflammatory reaction, and when rupture has occurred there are no reactive inflammatory lesions of the peritoneum, showing that the perforation occurred after death:

ALTERATIONS IN POSITION AND SIZE

Alterations in Position.—The stomach may be displaced into the thoracic cavity in cases of perforation or rupture of the diaphragm (*diaphragmatic hernia*). It may be displaced anteriorly as a congenital malposition in consequence of defects of the anterior abdominal walls, and may in such cases be quite exposed. Downward dislocation, or *gastroptosis*, is either congenital or acquired. The acquired form may be due to diseases of the stomach, particularly dilatation, to the traction of inflammatory adhesions, to enlargement of the spleen, and probably to tight lacing. Occasionally in anemic and relaxed women all of the abdominal viscera tend to descend (*splanchnoptosis*).

Dilatation, or gastrectasia, most frequently results from obstruction of the pylorus. The latter may be due to cicatrization the result of the healing of ulcers, to fibroid overgrowth and contraction the result of chronic gastritis, or to pyloric carcinoma. The pressure of tumors, of a movable kidney, or of aneurysms may act similarly. At first, pyloric stenosis may be compensated by hypertrophy of the muscular layer of the stomach, but soon dilatation occurs; food stagnates, fermentation takes place, and the dilatation is increased. The mucosa becomes thin and oftentimes degenerated and atrophic, the exact changes being those of the specific variety of gastritis existing.

A second group of cases (*atonic dilatation*) is independent of stenosis of the pylorus, but due to weakness of the walls of the stomach. The latter may be the result of chronic gastritis or of a general atonic state. Constant overeating may play an important part in some cases. Finally, dilatation may result mechanically from abnormal adhesions of the stomach.

Dilatation of the stomach occasions great stagnation of food and, in consequence, imperfect digestion and decomposition of the food. When hydrochloric acid is absent (as in cancerous stenosis of the pylorus and marked atonic dilatation) lactic acid fermentation is pronounced; when hydrochloric acid is present lactic acid is less abundant or absent. Sulphuretted hydrogen and inflammable gases are occasionally formed, especially in cases in which hydrochloric acid is present. The mucous membrane of dilated stomachs loses its absorptive power to a large degree. This, together with the retention of ingested liquid in the stom-

ach and the consequent lessening of intestinal absorption, leads to great emaciation, and especially to desiccation of the tissues. The muscularis shows hyaline change and thinning, with elongation of the fibers. The mucosa shows atrophic glands, with fatty cells.

Among the micro-organisms met with in the gastric contents the *Sarcina ventriculi* are of interest. These occur in bundles of peculiar square form. The sarcina is more frequent in non-cancerous than in cancerous dilatation. In cases of dilatation due to cancer of the stomach the Oppler-Boas bacillus is found (see below).

An acute form of gastric dilatation sometimes occurs after anesthesia, following indiscretions in diet, as a result of pressure on the duodenum when the mesentery is pulled upon by twists of the intestine, after traumatism, and at times without demonstrable cause. The most frequent anatomical factor is twisting of the intestinal loops, especially in the presence of an abnormally long mesentery. The method of action of these causes is not clear, but they probably operate by paralyzing the gastric wall.

INFECTIOUS DISEASES

A few cases of *tuberculous ulceration* have been recorded, and *syphilitic gummata* or *ulceration* may occur. The tuberculous processes may be hematogenic or localized, in which latter case they are secondary to peptic ulcer; they assume a ragged, punched-out appearance and seldom perforate. Diffuse cirrhosis and ordinary gastritis may be dependent upon syphilis, but the etiological connection is uncertain. *Anthrax* may lead to necrotic and hemorrhagic ulcers of the mucosa. *Thrush* is rarely met with, though the spores of the *saccharomyces* are frequently present in the stomach when the mouth is affected.

TUMORS

Connective-tissue Tumors.—*Fibroma*, *myoma*, and *lipoma* are occasionally met with as submucous or subserous polypoidal tumors. *Sarcoma* is rare. It affects the lymphoid tissues of the deeper parts of the mucosa, and rapidly spreads to the submucosa. Most cases are of the round-cell variety. Lymphoid infiltrates of the adenoid tissues of the stomach may be one of the lesions of leukemia or Hodgkin's disease.

Epithelial Tumors.—*Polypoid elevations*, sometimes with cystic enlargement of the glands, occur as a result of chronic inflammation, and may be large enough to be regarded as tumors in a clinical sense. *Adenomatous proliferation* of the glands is met with in the form of irregular, flat tumors, but these so rapidly become carcinomatous that pure adenoma scarcely exists.

Carcinoma is the most frequent tumor of the stomach. It occurs at middle age, and more often in the male sex than in the female. The pyloric end of the organ and the lesser curvature are the favorite sites, but other parts may be affected and the entire organ may be involved. Cancer of the stomach may appear as a ring-like swelling of the

mucous membrane and submucous tissue, surrounding the pylorus and causing stenosis; as more or less circular, flat elevations in the lesser curvature or elsewhere; and, finally, as a diffuse infiltration of the mucosa, submucosa, or all of the coats of the entire organ. The mucous surface is generally irregularly elevated, and tends to become ulcerated, especially in medullary cancer and in the cases in which there are localized flat elevations. Sometimes portions of the cancerous tissue may be found in the vomitus, and the diagnosis of the disease may be thus established (Fig. 272). Perforation of the wall of the stomach may result from necrotic and ulcerative processes (Fig. 273). The neighboring lymphatic glands, especially those in the lesser curvature of the

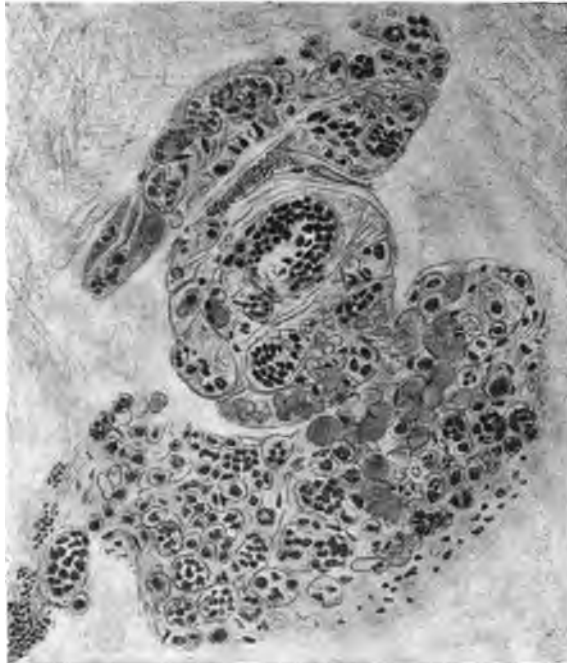


Fig. 272.—Fragment of carcinomatous tissue found in stomach-washings (Reinevoth).

stomach, are usually implicated through the lymphatic vessels. Direct extension to the peritoneum may occur, especially in cases of colloid cancer; and metastasis through the blood-vessels is extremely common. Cancerous emboli are frequently found in the portal radicles within the liver, and multiple cancer-nodes of the liver are usually found in cases which have existed for some length of time. Hematogenous metastasis is most common in soft, ulcerating cancers.

Varieties.—There may be distinguished *hard or scirrhus cancers*, *soft or medullary cancers*, *adenocarcinomata* or *malignant adenomata*, and *cylindrical-celled* or *squamous-celled carcinomata*. All forms begin in the mucous membrane and spread to the submucosa. The muscu-

laris may be penetrated and infiltration of the serosa, or even of surrounding tissues, may be observed.

Scirrhus cancer may appear as a circular constricting new growth at the pylorus (Fig. 274). In other cases the disease is extensive, and



Fig. 273.—Carcinoma of the cardiac end of the stomach; extension into duodenum: *S*, Dilated esophagus; *K*, ulcerated carcinoma; *G*, a perforating ulceration; *M*, stomach (Orth).

the entire organ may be involved by uniform infiltration, and macroscopically the appearance of a simple cirrhosis of the stomach is presented. In the last-mentioned variety the organ may be greatly reduced in size, though the walls are greatly thickened. The mucous surface rarely ulcerates in scirrhus.



Fig. 274.—Scirrhus of the pylorus, causing pyloric stenosis: *D*, Duodenum; *P*, pylorus; *K*, carcinomatous projections on the mucosa (Orth).

Medullary or soft cancer usually appears as a localized tumor at the pylorus or in the lesser curvature. The mucous membrane is irregularly elevated, oftentimes in a cauliflower manner (Fig. 275). Ulceration on the surface is common, and hemorrhagic extravasation into the

stomach is, therefore, frequent. Metastasis through the blood is liable to occur. Complete perforation of the stomach may take place.

Malignant adenoma, or adenocarcinoma, begins as a proliferation of gastric tubules. The new-formed acini are, however, atypical in arrangement and number, and there is a tendency to conversion of the normal cylindrical cells into cuboidal cells, and to extensive cancerous infiltration by excessive formation of acini or tubules, as well as by destruction of the basement-membrane of the acini and irregular cellular invasion. The appearance of the tumor and its tendencies are the same as those of soft cancer.

Cylindrical cancer, or cylindrical epithelioma, probably arises from the cylindrical lining cells of the stomach, or from the cells in the upper parts of the tubules. Atypical tubular aggregations of cylindrical cells with a tendency to conversion into cuboidal cells are observed. The pylorus is the common seat.

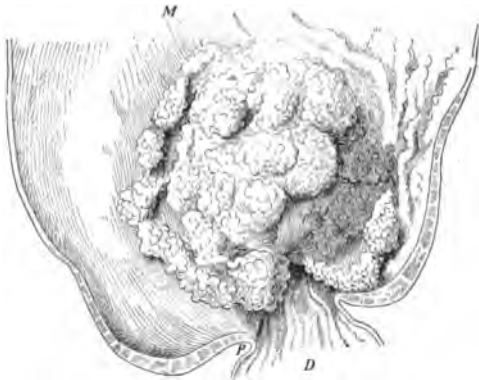


Fig. 275.—Cauliflower carcinoma of pylorus: *M*, Stomach; *P*, pylorus; *D*, duodenum (Orth).

Squamous cancer occurs at the cardiac end, and generally in association with carcinoma of the lower end of the esophagus, from which the squamous epithelium extends a short distance into the stomach. It is rare.

Colloid cancer of the stomach appears as a localized or, more frequently, diffuse infiltrating, gelatinous new growth of the mucosa and submucosa. Rapid extension through the walls of the stomach and to the peritoneum is frequent. The cells and the stroma of the tumor show myxomatous degeneration; and the epithelial elements may in the later stages entirely disappear. Extensive invasion of the peritoneum is not infrequent.

Pathological Physiology and Results.—Carcinoma of the stomach is most frequently situated at or near the pylorus, and, therefore, interferes with the propulsion of food. Stagnation of the stomach contents and fermentation result. The latter is favored by the absence of hydrochloric acid secretion so habitually observed. In consequence of the

stagnation the stomach dilates and may reach enormous size, not rarely filling a large part of the abdominal cavity. Lactic acid fermentation is frequently pronounced. Disturbances of metabolism, with loss of flesh and strength, are marked. Among the micro-organisms present in the stomach contents a long, thread-like bacillus (Oppler-Boas) has attracted much attention, and has been supposed by some to occur only in cancer of the stomach. It is certainly frequent, but just as certainly not peculiar to the disease.

THE INTESTINES

CONGENITAL AND ACQUIRED ABNORMALITIES

Occasionally *total absence* of large parts of the intestinal tract is found in monstrosities. Lesser defects, leading to *narrowing* or *distortion* of the intestines, are more frequent. Marked developmental defects most frequently occur in the rectum, which may be completely absent, or may be obliterated at the lower end. In such cases there may be fistulous communications with the urogenital tract, or there may be a persistent cloaca, as in fetal life.

Congenital Enlargement of the Intestines.—The colon is most apt to be affected, and may be greatly enlarged, the most important example of which is Hirschsprung's disease or megacolon. This may affect the whole colon or only the descending part. By some, atony or incompleteness of the musculature is held responsible, while others look upon it as obstructive from abnormalities in the mesocolon.

Diverticula.—Localized dilatations, constituting diverticula, are frequent, the most common form being *Meckel's diverticulum*. This usually arises from the ileum, about 1 meter above the ileocecal valve, and is attached to the intestine opposite the mesentery. It represents the remains of the omphalomesenteric duct of fetal life. Occasionally it has been found patulous to the umbilicus. More commonly there is merely a short diverticulum of the intestines, varying from a few to several centimeters in length, and having a closed extremity which may be somewhat dilated. The extremity may be connected with the umbilicus by a cord, but is usually free.

Diverticula are also formed in later life. Very commonly, in cases of constipation, small pouchings or dilatations occur in the large intestine, particularly in the descending colon and rectum. Another form affects the small intestine more commonly than the large bowel. In this there are found small pouches lying near the mesenteric attachment, and owing their origin to localized weakness or separation of the muscle-fibers of the bowel. Protrusion of the mucosa takes place, probably as a result of pressure from within; and the pouch is, therefore, a hernia-like projection of the mucosa and serosa through separated muscular fibers. Such diverticula may be multiple or single.

The importance of the diverticula, especially the Meckel variety, is that they may be involved in inflammation which may lead to per-

foration or to adhesions. In the latter case coils of intestines may be constricted and lead to ileus. Meckel's diverticulum, when not inflamed but if attached at the umbilicus, sometimes catches a knuckle of gut and leads to intestinal obstruction.

Congenital Abnormalities in Position.—The position of the several parts of the intestinal tract may vary widely from the normal. Not rarely the ascending colon and cecum are situated on the left side; the sigmoid flexure and descending colon being on the right side.

Cecum mobile is an abnormal looseness of cecum, sometimes leading to surgical conditions in this organ or the appendix.

Enterocystoma.—A congenital cystic condition found at the umbilicus has been described as cystic dilatation of parts of the original omphalomesenteric system of the fetus, and has been named "enterocystoma."

Dilatation.—More or less uniform enlargement of the intestines may result from long-standing constipation. Enormous dilatation of the colon is sometimes seen. In this the wall of the intestine undergoes compensatory hypertrophy, and small pouchings or diverticula are commonly observed, especially in the rectum.

This is the chronic dilatation. Acute dilatation is due to sudden obstruction, as from a foreign body or by paresis of the muscular wall, as occurs by blows on the abdomen. Again, the dilatation may be acute, but not necessarily sudden, when the gut walls are paralyzed by peritonitis or by toxins of diseases not localized to the abdomen (meningitis). Acute dilatation occurs in surgical shock.

Narrowing, or stenosis, of the intestine at any part may be due to pressure of new growths or displaced viscera, to cicatricial constrictions following ulcerations, or to neoplasms. Cicatricial stenosis is particularly common in the rectum following dysenteric or syphilitic ulcers. Narrowing of the lumen may be due to an ingrowth of carcinoma or the presence of papillomatous or polypoid tumors within.

Hernia.—This term is applied to malposition of any of the viscera, with displacement of the organ from the cavity in which it normally lies; but it has been more particularly applied to such displacements of the intestines, and the single term "hernia" is significant of intestinal hernia.

Occasionally herniæ are congenital; more often they are acquired. Hernia occurs at the points where the abdominal wall or the peritoneum is naturally weak from the emergence of vessels or the existence of natural outlets, or has become weakened by injury or surgical operation.

Etiology.—The predisposition to hernia may consist in unnatural weakness of the abdominal wall, especially at the points where hernia is likely to occur, resulting from imperfect closure of such portions or from general muscular weakness. Abnormal movability of the intestines, resulting from natural or acquired elongation of the mesenteric attachments and increased weight of the abdominal contents from the deposit of peritoneal fat, contributes largely to the formation of herniæ. The immediate exciting cause in many cases is strain, and probably in all

cases repeated strain helps in the development of the protrusion. The most frequent form of ventral hernia is the umbilical, which occurs especially in infants as the result of imperfect closure of the abdominal walls at the umbilicus.

There may be distinguished two groups or varieties—the internal and the external herniæ.

Internal Hernia.—By this term are designated hernia-like displacements of the intestines into other cavities within the body, the most important being upward displacement into the thorax through congenital or acquired clefts of the diaphragm (*diaphragmatic hernia*); and backward displacement through the peritoneum into the retroperitoneal space (*retroperitoneal hernia*).

External hernia may be *inguinal, femoral, ventral, vaginal, rectal, perineal, ischiatic, or obturator*. The most frequent of these are the inguinal and the femoral. In the former the protrusion may occur through the external inguinal ring, the intestine descending through the inguinal canal, sometimes as far as the scrotum (*indirect inguinal hernia*). In another group of cases the intestine pushes directly forward through the abdominal wall and external inguinal ring, and may present anteriorly under the skin, or may descend through the lower part of the inguinal canal to the scrotum (*direct inguinal hernia*). The indirect inguinal herniæ are sometimes congenital, and are due to the failure of closure of the peritoneal reflection which passes downward through the inguinal canal.

Femoral herniæ are especially common in women, and are formed by protrusion of the intestine through the femoral ring, the hernia presenting on the inner side of the thigh, at the position of the saphenous opening.

Pathological Anatomy.—The hernia consists of a sac or wall and of the contents of the hernia. The sac is usually constricted at its junction with the general peritoneal cavity (neck), and distended and dilated outside of or below this point (fundus or body of sac). The sac of the hernia is always lined with the protruded portion of the peritoneum. The contents of the hernia may be coils of intestine or portions of omentum, or both. Most frequently some part of the small intestine occupies the hernia, and sometimes simply a Meckel's diverticulum has been discovered. In rare cases the sigmoid flexure or other parts of the great bowel may be found.

Secondary changes often ensue. Inflammation of the lining membrane of the sac and of the intestinal coils may lead to fibrous adhesions constricting the neck of the sac and binding the intestines firmly in place. If the contents of the hernia have receded, such inflammation may obliterate the sac completely or merely at its neck, the body of the sac in the latter case becoming distended with serous liquid. In cases in which portions of omentum are included in the hernia, hypertrophic overgrowth of the adipose tissue may occur, and may lead to appearances not unlike those of a lipoma.

Herniæ are described as being *reducible* and *irreducible*, according to the ability of replacing the contents into the peritoneal cavity or not.

Herniæ become irreducible when the coils of intestine are distended by the accumulation of fecal matter, when fibrous adhesions have narrowed the neck of the sac or bound the coils firmly in place, or when additional coils of intestine or portions of the omentum have descended into the hernia.

Strangulated Hernia.—This term is applied to herniæ in which pressure at the neck by inflammatory exudation or constriction, or inveterate obstruction by accumulating contents of the bowel, has led to obstruction of the circulation in the intestinal coils of the hernia. Intense passive congestion, inflammation of the peritoneal covering of the intestines within the hernia, and, finally, gangrenous necrosis are the frequent results.

INTESTINAL OBSTRUCTION

Complete obstruction of the intestines, or ileus, may be due to internal strangulation by bands of adhesions, to a twist or volvulus, or to intussusception or invagination.

Internal strangulation may be due to the obstruction of a coil of intestine by fibrous peritoneal adhesions, or by a coil slipping through abnormal openings or perforations in the mesentery or omentum. The persistence of the cord passing from the end of a Meckel's diverticulum to the umbilicus is an unusual cause.

The results of internal strangulation are generally serious. Great dilatation occurs above the point of obstruction, the intestine below becoming collapsed. Great congestion and subsequently peritonitis occur at the point of stricture, and necrosis with perforation may ensue. The constitutional symptoms may be due to absorption of toxic substances developed in the strangulated parts, that is, in the gut walls by autolysis. The results are essentially the same for obstruction of all parts of the intestines, but appear more rapidly when the upper parts are affected. The loss of water is due to drainage of large quantities into the gut lumen. These theories hold for all forms of obstruction, including the postoperative intestinal paresis.

Volvulus is the term applied to a twist of some part of the intestinal canal. Occasionally there is simple rotation of the bowel about its own axis, but more commonly a loop of intestine twists about on its mesenteric attachment. Abnormal laxity of the mesentery is an important predisposing cause, and may be a congenital condition, or may result from the absorption of fatty deposit between the mesenteric layers. The immediate cause is generally strain or abdominal compression.

The most frequent seat of volvulus is the sigmoid flexure. The bowel above the point of obstruction becomes distended, as in internal strangulation, while the coil included in the twist itself is engorged with blood and often presents hemorrhagic infarctions in consequence of obstruction of the veins in the mesentery. Gangrene of the bowel may result. Complete knots are occasionally observed in volvulus.

Intussusception, or invagination, is a condition in which one part of intestine slips into an adjoining part, as one may invert the finger of a glove (Fig. 276). The upper part of the intestine is usually indu-

plicated and pushed into the lower part. Irregular peristalsis, resulting from intestinal disorders, and particularly from atony of one part with increased activity of adjoining parts, is the most frequent cause, and continuing in the disturbed part further propels the outer over the inner segment, or *vice versâ*, as it would a mass of feces. Occasionally polypoid tumors within the bowel are dragged forward by the peristalsis, and carry the higher part of the intestine to which they are attached

into the lower part. Intussusception is more common in children than in adults, and affects the ileocecal region most commonly. Not infrequently multiple invaginations are found in the small intestine of children; these probably occur during the death agony or postmortem.

The portion of the gut slipping into the receiving part is called the *intussusceptum*; the outer or receiving section, the *intussusciens*.

The appearance of intussusception is simply that of one part of intestine pushed into the adjoining part, with secondary inflammatory and congestive changes. Most frequently invagination begins at the ileocecal region, the valve and ileum being carried forward into the ascending colon. Very rarely the ileum itself invaginates through the valve. The attachment of the mesentery leads to a sharp angulation of the area of invagination, and the extent to which the protrusion may occur will depend upon the length of the mesentery. Occasionally the ileocecal valve may be carried through the colon and rectum and present externally. The adjoining serous surfaces of the invagination tend to unite by peritonitis, and the intussuscepted portion may become gan-

grenous and be discharged with re-establishment of the lumen. If peritonitis has established union between the ensheathed and the ensheathing section of the gut, recovery may ensue. Otherwise perforation leads to fatal peritonitis.

PROLAPSE OF THE RECTUM

Prolapse of the rectum in consequence of weakness of the sphincter and other parts of the wall, together with repeated straining, is a common condition in infants, and is occasionally met with in adults. In children any form of diarrhea may be complicated by prolapse; in adults chronic proctitis is the most frequent cause. The weakened condition of the sphincter in proctitis furnishes the predisposition, and the characteristic tenesmus of the disease is the immediate cause. Prolapse may be only an occasional condition, or may be constant. Secondary inflammation, ulceration, and even necrosis of the prolapsed portion may occur.



Fig. 276.—Intussusception (from a specimen in the Museum of the Philadelphia Hospital).

ATROPHY AND DEGENERATIONS

Atrophy of the mucosa is frequently met with as a part of chronic enteritis in its later stages. This is especially marked in young children suffering from chronic intestinal catarrh and marasmus. Occasionally atrophy of the mucosa or of all of the coats of the intestines may occur as an independent affection, or as the result of marantic or cachectic conditions.

Pigmentation may be due to hemorrhages in the mucosa or submucosa, and not infrequently after intense hemorrhagic inflammation the bowel may be quite black from the deposit of hematogenous pigment. Brownish pigment deposited in the muscle-cells, analogous to that of brown atrophy of the heart, is occasionally observed in old and cachectic individuals. Similar pigmentation of the muscle-cells and also of the submucosa or mucosa, of even more decided character, occurs in youthful persons addicted to alcohol. The intestines alone may be thus affected, or the liver, spleen, lymphatic glands, and skin are simultaneously involved. The term *hemochromatosis* (*q. v.*) has been proposed for this condition. It is said that pigmentation of the colon may result from absorption of bile derivatives. Pick accounts for some of the obscure pigmentations of the colonic mucosa by assuming a deposit of melanin-like bodies, probably protein digestion products under the influence of tyrosinase.

Amyloid infiltration is met with in association with amyloid disease of the liver, kidneys, or spleen, and particularly in cases in which there is tuberculous ulceration of the intestines. The mucous membrane is principally involved, and becomes somewhat hardened and presents a peculiar grayish luster. Superficial erosions and even ulcers may result. The process begins, as elsewhere, in and around the small blood-vessels.

CIRCULATORY DISTURBANCES

Active hyperemia may occur from acute irritation, and forms a part of inflammation.

Passive hyperemia results from causes similar to those producing congestion of the stomach. Among these, obstructive diseases of the liver, notably cirrhosis, and cardiac and pulmonary affections are most prominent. The intestinal mucosa becomes somewhat swollen, oftentimes edematous, dark bluish-red in color, and occasionally marked by punctate hemorrhages. The mesenteric veins are widely dilated. Occasionally hemorrhagic liquid is found within the intestines, the points of hemorrhage remaining undiscovered.

Hemorrhage.—Petechiæ are found in many cases of violent septic or infectious diseases, in intense anemias, and as the result of marked passive hyperemia. Embolism in cases of ulcerative or malignant endocarditis may lead to petechial hemorrhages, and the same are observed as a part of the morbid anatomy of intestinal anthrax. Large intestinal hemorrhages may occur from typhoid, tuberculous, dysenteric, or syph-

ilitic ulcerations, or from the perforation of a large arterial branch by a peptic ulcer in the duodenum. Hemorrhoids may occasion considerable hemorrhages from the rectum.

Edema of the mucosa may result from passive congestion, and attends acute or chronic inflammations, especially the more intense forms.

Embolism and thrombosis of the mesenteric arteries are rare conditions, due most often to cardiac embolism, but also to arteriosclerosis *in loco* and to downward thrombosis from the portal vein. Embolism may lead to hemorrhagic infarction because of some inadequacy of the anastomosis of the mesenteric vessels, which usually is rich. The result is a stretch of paralyzed, reddened, and swollen gut within which hemorrhage and, later, sloughing occur, corresponding to the distribution of the occluded vessel.

Hemorrhoids result from varicose enlargement of the veins of the rectum. They are usually found in the lower part of the rectum, inside or outside the sphincter, and a distinction is made between internal and external hemorrhoids.

Etiology.—Obstruction of the venous circulation is the important etiological factor. It may be due to chronic diseases of the liver (cirrhosis), repeated pregnancies, pelvic tumors, or chronic constipation with frequent retention of feces in the rectum. The last-named condition acts in a twofold manner. On the one hand, it causes venous obstruction, and, on the other hand, chronic proctitis, which in turn occasions disease of the veins of the rectum, and thus predisposes them to dilatation. In all cases of hemorrhoids, constipation and the resulting proctitis are important as auxiliary causes. The anal veins are poorly supported by connective tissue, so that when the sphincter contracts it holds the blood within the distended vessels. Hemorrhoids are rarely met with before adult age.

Pathological Anatomy.—The hemorrhoid presents itself as a small polypoid elevation of more or less congested appearance. On section it is found to be highly vascular and to consist of dilated veins. There may be a congeries of slightly enlarged veins or cavities of considerable size. Between the veins there is more or less abundant inflammatory connective tissue. Thrombosis often occurs within the cavities; and occasionally the fibrous tissue around them undergoes active proliferation, when a structure resembling a fibro-angioma results. Hemorrhagic extravasations may occur from the veins, and free hemorrhage from the surface is a common symptom. Infective inflammation and phlebitis of the veins sometimes occur, in which cases the hemorrhoid enlarges and becomes inflamed and edematous. Inflammation of the adjoining tissues may occur (proctitis, periproctitis).

Hemorrhoids may cause marked anemia by the repeated hemorrhages, and sometimes occasion septic infections when they have themselves become infected and inflamed.

Other varices may arise in the intestines, as, for example, in cirrhosis of the liver.

INFLAMMATIONS

Inflammation of the intestines, or enteritis, may affect any part of the intestinal canal, and involve the mucosa and submucosa more particularly. It is more frequently present in children and in the aged than at other periods of life.

Etiology.—The causes of enteritis are similar to those of gastritis, and among them may be reckoned all forms of irritating foods or foreign matter taken with the food. Poisons of various kinds operate in a similar manner. In many cases the irritant poisons which occasion enteritis are developed within the body in consequence of improper digestion and fermentation. Bacteria play an important rôle in this process, and are themselves the direct cause of enteritis in instances in which improprieties of diet or digestive disturbances have furnished favorable conditions for their growth and multiplication. The normal colon bacillus is perhaps the most frequent and important micro-organism of ordinary non-specific enteritis, but other organisms doubtless frequently play a part. The colon bacillus probably increases in virulence under certain conditions and then occasions irritation.

The bacteria of the intestines comprise many species, chiefly saprophytic, but which may under appropriate circumstances cause enteritis. They are engaged in fermentation and putrefaction, the two forces being balanced in the normal state. When, however, one or the other is excessive, it reduces the natural protective forces. The normal intestinal wall and juice are protective, but if disturbed are attacked either by the normally present germs or others to whose entrance in food the damaged organ offers no resistance. The mechanical conditions mentioned in the discussion of bacteria in the stomach play a similar rôle in the intestines.

Pathological Anatomy.—There are a number of varieties of enteritis, and different types may be described, though individual cases rarely conform to a single variety. Of the acute forms of enteritis, the important are the catarrhal, suppurative, and the pseudomembranous.

Catarrhal enteritis may affect any part of the intestinal tract. The mucosa is swollen and usually light-red in color; the arteries are visibly distended, and not rarely there are petechial hemorrhages. The surface is covered with mucous exudate containing desquamated and degenerated epithelial cells and emigrated leukocytes; while the intestinal contents are rendered liquid by serous exudation. The solitary follicles or agminated collections of lymphoid tissue may be particularly swollen and cause projections above the surrounding mucosa. The term *follicular enteritis* is applied to such cases (Fig. 277). In other instances the desquamation of epithelium is more prominent than the mucous exudation, and considerable shreds of mucosa may be loosened and discharged. The term *croupous enteritis* is suggested by such conditions.

The so-called *toxic enteritis*, such as is seen in toxic (not bacterial) meat-poisoning, is of the catarrhal type, with much hyperemia and edema. Superficial necrosis or hemorrhage may occur.

Suppurative enteritis differs from the catarrhal form in the greater degree of emigration of leukocytes. The exudate upon the surface may be largely composed of white corpuscles, and in intense cases the surface may be covered with almost pure pus. Round-cell infiltration of the mucosa and the submucosa is present, and focal collections leading to *submucous abscesses* or to *ulcers* upon the mucous surface are occasionally seen. The solitary follicles are enlarged and tend to break down, forming *follicular ulcers*.

Pseudomembranous enteritis is characterized by the formation of a grayish membrane upon the surface of the intestine. The large intestine is more frequently involved, and the process is especially met with in dysentery (see p. 639). True diphtheria of the bowel with pseudomembranous deposit may sometimes occur.

The term *ulcerative enteritis* is sometimes used, but, as a matter of fact, non-specific ulcerations are relatively rare. Erosions are commoner. It is better to speak of the pathological type of enteritis with ulceration,

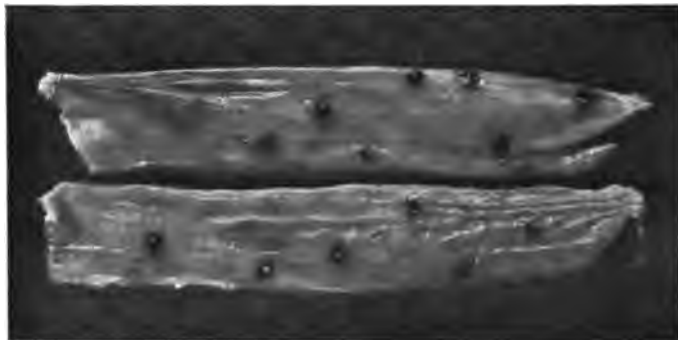


Fig. 277.—Hemorrhagic follicular enteritis.

as the ulcerative forms are considered under typhoid, tuberculosis, and the like. Ulceration of the intestines occurs in a variety of conditions. *Peptic ulcers*, similar to those met with in the stomach (*q. v.*), are occasionally found in the duodenum, and are there explained as given for gastric round ulcer. They have the same characters and tendencies as those of the stomach; they may occasion sudden death from hemorrhage. Ulcers in the duodenum are also an occasional result of extensive burns of the skin; and attention has been called to the frequency of duodenal ulceration in cases of chronic Bright's disease. Ulcerations of the ileum are habitual in typhoid fever and tuberculous enteritis, and are occasionally due to anthrax or actinomycosis. Ulcers may be found in all forms of enteritis of childhood, especially in intense forms and in cases complicating the exanthemata. Sarcomata and carcinomata are rare causes. Ulcerations of the large bowel are met with in chronic colitis and dysentery. A form of peculiar clinical interest is *anal fissure*. This is a linear ulceration of the rectum in the region of the sphincter. It may be associated with hemorrhoids or may be independent.

Chronic enteritis results from acute attacks or from repeated irritation. Chronic congestion in consequence of hepatic or cardiac affections is a predisposing cause of importance.

In the early stages the mucous membrane is usually more or less swollen, and sometimes proliferative changes in the glandular elements may lead to distinct polypoid elevations. These are especially pronounced in cases in which the healing of ulcers of acute enteritis has occasioned cicatricial constrictions and thus elevated adjoining parts of the mucosa. The elevated portions may undergo proliferative inflammation, and polypoid formations result. In the later stages of chronic enteritis atrophy may ensue, in part as the result of the overgrowth of the stroma of the mucosa and the degeneration of the glandular elements, in part also as the result of the overdistention or tympany resulting from fermentation of the intestinal contents. This atrophy may affect the mucous membrane alone, but more commonly also involves the muscularis. Hyperplastic processes in the lymphoid elements may be a prominent feature in the hypertrophic stage of chronic enteritis, and may give place to atrophy in the later stages. On the other hand, the enlargement of the solitary follicles and Peyer's patches may persist for a long time after atrophy has led to great thinning of the remaining portions of the mucosa.

Pathological Physiology.—Enteritis may occasion profound disturbances in a variety of ways. In cases of infective character general systemic intoxication may result from the absorption of bacterial products or substances resulting from decomposition of the intestinal contents. In other cases the intensity of the local irritation may, through the nervous system, occasion great depression or shock; and subsequently the exudations into the intestines may cause depletion of the vascular system and failure of the circulation. The local effects and the resulting behavior of the bowels differ in different cases. Sometimes the peristaltic movements are arrested by the intensity of irritation and obstinate constipation results; more frequently hurried peristalsis and the abnormal exudation (serous or mucous) occasion diarrhea. The digestive processes fail from the diseased condition of the bowel, as well as from the rapid peristalsis and premature discharge of the intestinal contents; more or less profound disturbance of health results.

INFLAMMATIONS OF SPECIAL PARTS

Duodenitis occurs in association with gastritis from irritating food and the like. The appearances are the same as in gastritis. Duodenitis is prone to occasion obstruction of the terminal portion of the common bile-duct by the inflammatory thickening of the mucosa and the accumulation of mucus in the mouth of the duct; and in this way gives rise to obstructive jaundice (*catarrhal jaundice*). The inflammation may extend into the liver or pancreas along the respective ducts.

Inflammation of the ileum presents no special characteristics, excepting that enlargement of the follicles (*follicular enteritis*) is fre-

quently conspicuous. Follicular ileitis is particularly common in children suffering from infectious fevers, such as diphtheria and scarlatina. Peyer's patches may be considerably enlarged and even ulcerated. The ulcers are generally small, and several may occur in a single Peyer's patch instead of single ulcers, such as occur in typhoid or tuberculous enteritis. It is a curious fact that some of the lymph-follicles may be free from gross alterations even in severe follicular enteritis.

Typhlitis or **cecitis** (inflammation of the cecum) may be due to the irritation of the intestinal contents in consequence of constipation (*stercoral typhlitis*). This affection is probably very frequent, though it leads to no severe consequences and occasions no urgent symptoms. Typhlitis is probably generally of the simple catarrhal variety, but in obstinate constipation or obstruction of the colon ulceration may occur. Perforation or extension to the surrounding tissues (*perityphlitis*) is the rarest of all consequences. Usually the latter is secondary to inflammations of the appendix vermiformis.

Appendicitis may be a primary condition, or it may result from primary typhlitis or cecitis. The inflammation of the mucosa of the cecum may extend directly to that of the appendix; or may cause obstruction of the mouth of the appendix in the same manner as duodenitis causes obstruction of the common bile-duct. There results a retention of the contents of the appendix and multiplication with increase in virulence of the contained bacteria (*Bacillus coli communis*, staphylococcus, streptococcus, and others). The mucosa of the appendix, rendered less resistant in consequence of the overdistention and associated congestion, may be penetrated by the micro-organisms and appendicitis results. There may be some slight defect in the surface epithelium into which the bacteria pass. Superficially there is little change, but it is characteristic of the appendix that lesions spread into the deep layers to a greater extent than on the surface. This deep spread is probably due to early if not primary involvement of the lymph tissue, which in swelling obstructs the lumen of the tube and creates recesses within which bacteria multiply. In many cases fecal concretions are found within the appendix, and less commonly foreign bodies of various sorts have been found. These have been assumed to be the direct cause of the disease, and doubtless may play a part by irritating the mucosa, or injuring it in such manner that micro-organisms easily penetrate it. On the other hand, there is much reason to believe that the fecal concretions are often formed in consequence of the accumulation of mucous and desquamated epithelial cells and the stagnation of the contents of the appendix, after the disease has begun. The position of the appendix and rapid swelling of its mucosa favor retention of foreign bodies and exudates, while its movability renders kinking easy. Typhoid and tuberculous ulcers and actinomycosis have been found in the appendix. These lesions may occasion secondary appendicitis of an ordinary sort, or they may in themselves cause the symptoms of appendicitis. Obstruction of the arterial supply of the appendix was formerly regarded as an important element in the etiology, but probably is only of secondary im-

portance. Appendicitis is less frequent in women than in men. This has been ascribed to the existence of a more adequate blood-supply (the supplemental part derived from the ovary) in women.

The **pathological anatomy** of appendicitis varies in different cases, and we may, for convenience, distinguish a *catarrhal*, a *necrotic* or *gangrenous*, and an *interstitial* form.

In the mildest or catarrhal form there is merely retention of the contents of the appendix and slight disease (swelling and erosion) of the mucosa. The muscularis and serous coat may be congested and edematous, but are not extensively involved. The contents of the appendix are more or less mucopurulent in character, and may, of course, become pure pus.

In the necrotic or gangrenous form the mucous membrane suffers rapid destruction and the muscular and serous coats are quickly invaded. Fibrinous peritonitis soon develops in the serous coat and over the adjacent intestines, either as a result of penetration of bacteria through the walls of the appendix, or in consequence of perforation of the walls. The local peritonitis serves the purpose of restraining the infective disease and prevents diffuse peritonitis. In cases of rapid gangrene, with early rupture or escape of abundant bacteria, general peritonitis may result before a restraining wall can be formed.

The term "interstitial appendicitis" may be used to designate cases in which all of the coats of the appendix are involved and in which there is a special tendency to productive changes in the connective tissues. In reality, all cases of appendicitis show more or less interstitial change of this character (Fig. 278); but in some it is the conspicuous feature. These cases frequently terminate in chronic thickening of the appendix.

Results.—Mild cases of catarrhal appendicitis may subside after free purgation, with relief of the obstruction at the mouth of the appendix. In more serious inflammations and in cases in which the ob-

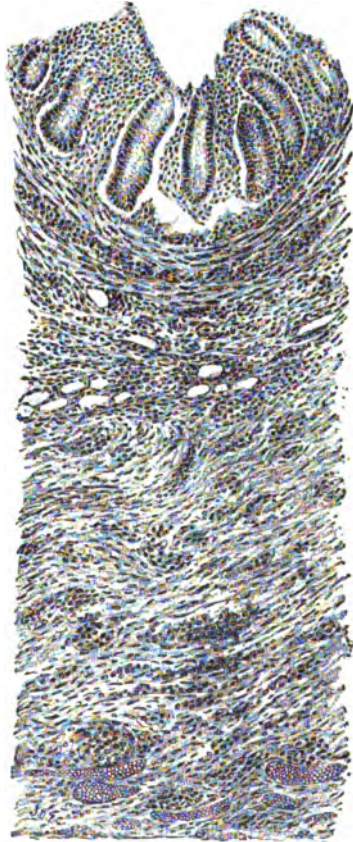


Fig. 278.—Acute appendicitis, with round-cell infiltration and hyperplasia of connective tissue in all of the coats. In large part the round cells of the mucosa and submucosa belong to the normal lymphoid tissue of these parts.

struction remains, the disease spreads through the walls of the appendix to the peritoneum and occasions local peritonitis; or rupture of the appendix occurs, and more intense local or general peritonitis follows (Figs. 279-281). In either case fibrinous deposits are formed upon the peritoneum, and not rarely a localized abscess (*periappendiceal abscess*) results. The appendix itself may be separated from the cecum, and may lie free in the abscess, or it may be firmly embedded in the fibrinous wall of the abscess. The latter may subsequently undergo inspissation, but more commonly ruptures into the general peritoneal cavity, into some part of the intestines, into the ureter, bladder, or externally. In cases with favorable outcome the appendix is usually bound down by adhesions which attach it to neighboring coils of intestine or to other structures. The appendix in such cases is usually distorted and greatly thickened, and repeated attacks of inflammation (*relapsing or recurring*

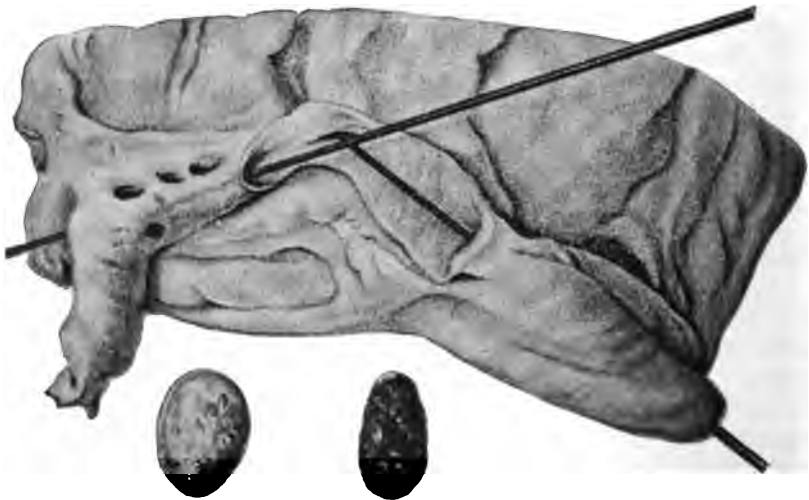


Fig. 279-281.—Ulcerative and perforative appendicitis, showing perforations; two fecal concretions from other cases of appendicitis (modified from Bollinger).

appendicitis) are not unusual. Chronic appendicitis may arise in this manner, that is, as a remnant from an acute process; but it also occurs without involvement of the peritoneum, the lesions being confined to the appendiceal mucous and muscular layers. Chronic appendicitis may be divided into the catarrhal and sclerosing forms. In the former type we have alterations in the structure of the inner coats as the most prominent change, while in the sclerotic form connective-tissue overgrowth occurs throughout all coats, so that finally, by contraction, the glandular structures are destroyed, and the organ becomes a fibrous cord (*obliterating appendicitis*).

There is generally more or less systemic intoxication and infection with appendicitis, and degenerative changes and metastatic abscesses may be found in distant organs. Not rarely pyelophlebitis and metastatic abscesses of the liver are encountered.

Colitis, aside from the specific form (dysentery), is most frequently due to irritation by fecal accumulations, and the sigmoid flexure is the common seat. The entire colon may, however, be involved. It may assume catarrhal, ulcerative, or pseudomembranous forms, the most conspicuous of the last being "mucous colitis." Thickening of the mucous membrane and abundant exudation of mucus are the prominent features of the earlier stages; while in the later stages atrophy and thinning are observed. Ulcerations are not uncommon. When the mucous exudation and the desquamated cells accumulate upon the surface the appearance of a pseudomembrane is simulated, and casts of the bowel or masses of mucus may be discharged from time to time. The other forms of colitis are in no manner peculiar.

Proctitis, or inflammation of the rectum, may be due to direct irritation by retention of fecal matter, by parasites, or by toxic agents; or it may occur secondarily after various other diseases of the rectum, such as tumors, hemorrhoids, and the like. The inflammation tends to become chronic. The rectum is generally involved with the colon in cases of mucous colitis.

The mucous membrane is considerably swollen, often edematous, and usually presents petechial hemorrhages. Ulceration may occur secondarily, and extension of the ulcerative process to the surrounding tissues (periproctitis) is not unusual. In the latter cases fistulous communication may be established between a perirectal abscess and the rectum (*incomplete fistula*), or a fistulous communication may form between the rectum and the exterior (*complete fistula in ano*). Sometimes proctitis is secondary to periproctitis occurring in diseases such as typhoid fever, pyemia, and the like.

INFECTIOUS DISEASES

Dysentery is a name applied to two varieties of infectious colitis whose etiology is now quite definitely accepted. One form, *bacillary dysentery*, is due to a non-motile bacillus of typhocolon morphology (see p. 297), while the other form, *amebic dysentery*, is caused by a protozoön, *Entamoeba histolytica* (see p. 365).

Bacillary dysentery is a communicable colitis, presenting acute, subacute, or chronic characters, due to one of the varieties of the *Bacillus dysenteriae*. It appears as epidemics in the tropics, in camps and institutions, or may occur sporadically. It seems to be a general infection in the acute cases, but there is rarely a bacteremia, except shortly before death. The bacteria may at times find their way to the lymph-glands draining the affected bowel. Rare instances of septicemia are reported. The hygiene and bacteriology have already been discussed.

The *morbid lesions* are usually confined to the colon, but may at times extend to the ileum. In the large gut the whole length is usually involved in, at first, a congestive and mucocatarrhal inflammation. This is rapidly overshadowed by a superficial necrosis which affects the tips of the rugæ. Great swelling of the mucosa enlarges and distorts these

folds. Over the mucous surface there appears a delicate necrotic film which can be rubbed away by the finger, leaving eroded or superficially ulcerated surfaces. The mucosa as a whole is swollen, but the process is more superficial than in amebic dysentery. In fulminating cases the mucosa becomes hemorrhagic or even gangrenous. In subacute and chronic cases these changes are not so intense, the follicles being more involved and becoming prominent.

Amebic dysentery is a communicable colitis, usually chronic, but at times acute, due to *Entamoeba histolytica*, endemic in some tropical and subtropical countries, occasionally appearing in epidemic or sporadic forms in higher latitudes, and showing a great tendency to involve the liver with abscess formation. It is commonest among white male adults.

The lesions are usually confined to the upper colon, although the sigmoid and rectum are often involved. When the amebæ penetrate the mucosa they infest the submucosa, causing great swelling and thickening by edema, round-cell infiltration, and proliferation of fixed tissue cells. This swelling interferes with the nutrition of the overlying mucosa, and ulceration is early and extensive; the infiltration is so widespread and rapid in its extension that intercommunicating swellings, and then undermined ulcerations, are produced. The ulcers are of all conceivable shapes, and as the infiltration or destruction in the submucosa is greater in extent than the loss of surface, mucous membrane bridges only may separate the surface's defects. Penetration to the muscular or serous coats is known, and perforation is sometimes seen. Healing occurs by granulation tissue, beginning around the base of the ulcer.

Microscopically, the infiltrate is of round and tissue cells, and few polynuclears are found. Eosinophiles are common. The characteristics of amebic dysentery are the marked infiltration and thickening of the submucosa, in which lie amebæ occupying spaces in the cellular collections, and in lymph- or small blood-vessels. The liver lesions consist of single or multiple abscesses or focal necroses with parenchymatous degenerations. Abscesses occur chiefly in the right lobe near the colonic or diaphragmatic surface. The contents vary from serous to a reddish-brown, puriform, necrotic material, in which, near the wall, amebæ may be found. This wall consists of a layer of dense tissue cell proliferation and infiltration of round cells, with great congestion about it. These abscesses may rupture, the commonest direction being through the diaphragm to pleura and lung.

Cholera.—Cholera epidemica or Asiatica is an acute specific inflammation of the small and large intestines due to the comma bacillus or vibrio of Koch. This micro-organism is found in the great majority of cases, but occasionally it is not discovered, while other micro-organisms, *Bacillus coli communis* and streptococci, are present. It is probable that in these instances errors of observation cause the failure of detection.

Pathological Anatomy.—Cholera is characterized by redness and swelling, and not rarely by petechial ecchymosis of the mucous mem-

brane, particularly of the small intestine (ileum). The superficial epithelium suffers early an extensive degeneration, perhaps a form of coagulation necrosis. The solitary follicles and the agminated glands may enlarge and may suffer ulceration. The intestines contain and discharge a serous exudation, often in large quantities, in which are grayish or whitish particles, consisting of flakes of desquamated and



Fig. 282.—Typhus abdominalis: medullary swelling.

Fig. 283.—Typhus abdominalis: ulcers with slough removed.

degenerated epithelium. The term “rice-water discharges” is applied to the evacuations. Extensive areas of the mucous membrane may be laid bare by the desquamation of the epithelium. When cholera has passed to its later stages, secondary pseudomembranous inflammation of the mucous membrane is not unusual, and is probably the result of secondary infection.

Associated Conditions.—The blood is thickened and dark red in color; thrombosis in the heart or venous sinuses is frequent. These are due to the great loss of water by the diarrhea. The kidneys present marked congestion and degeneration, which are dependent upon the action of the toxins of the disease. Lobular pneumonia is a common complication. There is apt to be a slight fibrinous peritonitis, while the gut itself is thin and atrophic.



Fig. 284.—Typhus abdominalis: superficial necrosis.

Typhoid fever is distinguished by an acute, specific inflammation of the lymphoid elements of the intestines, particularly of the ileum and upper portion of the colon (Figs. 282–285). The specific cause is the *Bacillus typhi abdominalis*, described by Eberth and Gaffky. This organism enters the gastro-intestinal tract with drinking-water, milk, or other food, and multiplies in the small intestine (see page 289).

Pathological Anatomy.—The specific lesions of typhoid fever occur in the lymphatic structures, notably in the solitary follicles, Peyer's patches, mesenteric glands, and spleen. It is, however, wise to remember that a few cases of typhoid bacillus infection giving a Widal reaction, but without intestinal lymph-gland ulcers, have been observed, or with only small atypical mucous membrane lesions. The bacteremia and parenchymatous lesions may be otherwise as typically described.

The solitary follicles and Peyer's patches of the lower end of the ileum are first affected, but later, or exceptionally in the beginning, the lymphoid collections of the upper part of the ileum and jejunum, or of the cecum and colon, may be involved. At first the follicles and patches are swollen and somewhat reddened by congestion. Within a few days of the onset, however, they lose their congested appearance and present themselves as grayish or white elevations projecting from one to several millimeters above the surface (Fig. 282). Microscopically, the lymphoid elements are found in a state of active proliferation, and,



Fig. 285.—Typhoid fever, showing necrosis of Peyer's patches and intense congestion of the bowel (modified from Kast and Rumpel).

in addition, large round cells (endothelioid) are more or less abundant. These large cells are actively phagocytic, and have been discovered in the lymphatic channels at some distance from the local lesions, as well as in the mesenteric glands and in distant parts. These cells increase in number, and may in some areas outnumber the small round cells. The surrounding mucosa may be normal in appearance or may be somewhat inflamed. The dense cellular packing gives a pale color to this stage of *medullary infiltration*, which remains unchanged for some days or a week. After the first week necrosis is prone to occur. The center of the solitary follicles or part of the Peyer's patch becomes more and more soft and yellow, or sometimes reddish from absorption of blood-pigment. The necrotic portions are discharged after a few days, leaving an ulcerated surface of regular or irregular outline, and presenting overhanging necrotic edges with hemorrhagic infiltration (Figs. 284–287). Sometimes not all of the swollen glands slough away, and a knobby or granular appearance results from the retention of isolated lymph-follicles.

The ulcers resulting from destruction of the solitary follicles are small and rounded, while those involving the Peyer's patches are elongated,



Fig. 286.—Typhoid fever. Swelling of lymph-follicles, cross-section of Peyer's patch (Karg and Schmorl).

gated, the long axis being parallel with the axis of the intestine. The bases are smooth except, perhaps, for muscular ridging. The ulcers

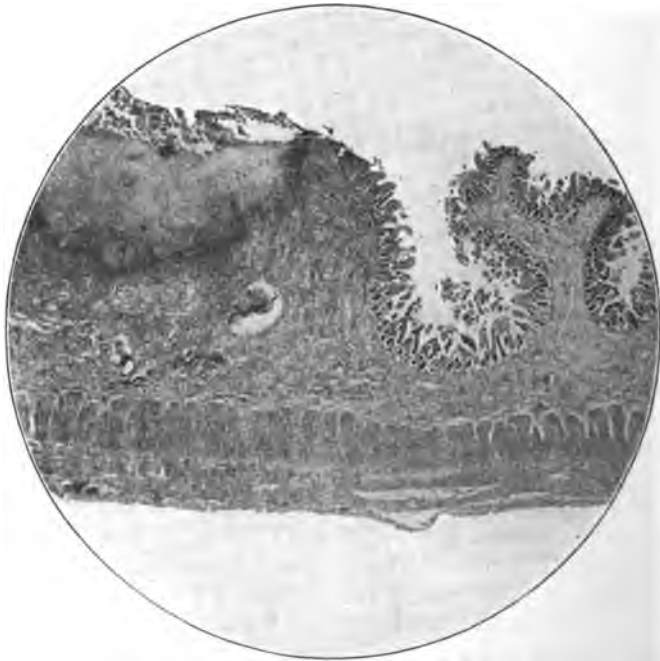


Fig. 287.—Typhoid fever, slough formation, showing edge of Peyer's patch becoming necrotic. The mucosa to the right shows catarrhal inflammation which usually accompanies the follicular lesions (Karg and Schmorl).

are usually found in an acute stage at the end of the second or at the beginning of the third week of the disease. Resolution may occur without necrosis and ulceration, but more commonly ulcers are formed and

healing proceeds more slowly. The lymphoid elements of the follicles and patches are usually permanently destroyed, and healing takes place by proliferation of the fibrous stroma. A covering for the bared muscle is made from the mucosa after the inflammatory swelling has left the edges of the ulcer. Occasionally, however, complete restitution of the normal tissues occurs. When the lymphoid follicles of the patches have become necrotic and have been infiltrated with blood, dark pigmented spots are formed, and give rise to the condition designated as the "shaven-beard" appearance.

Complications.—Extensive necrosis may lead to erosion of a blood-vessel and hemorrhage; or the wall of the intestine may be completely perforated by the necrotic process, and fatal peritonitis may result. In other instances peritonitis occurs without perforation by direct extension of the inflammatory process through the intestinal wall. Very commonly slight reactive peritonitis is found on the serous surface opposite the ulcers. Extensive peritonitis rarely occurs in this way. Peritonitis in rare instances results from necrosis of the mesentery glands, or from rupture of the spleen.

The mesenteric glands are characteristically enlarged, those nearest the points of ulceration being first and most prominently involved. In the first stage they are soft and dark red in color, exuding a small amount of liquid on section. Later, they become larger, harder, and of whitish appearance; they may finally suffer necrosis and rupture. Usually, however, resolution takes place after the first stage.

The spleen is enlarged in most cases, and presents the characteristics of acute splenic tumor. Very rarely perisplenitis or abscess may occur. In the bone-marrow there is an increase of the small round cells and large phagocytic endothelial cells.

The typhoid bacillus seems to have the power to stimulate the endothelial cells, for we now look upon the large cells of the lesions in Peyer's patches as endothelial, and certain it is that these cells, in lymph-glands, spleen, and bone-marrow, are found in great abundance. They are phagocytic for necrotic cells and bacilli.

Lesions in Other Parts.—The muscles, particularly those of the abdominal walls, frequently show spots of degeneration of a waxy or hyaline character, as described by Zenker. Very rarely petechial or considerable hemorrhages may be found in the muscles; and abscesses are sometimes met with as sequelæ.

The heart muscle is involved in perhaps a majority of the cases. The muscle-fibers suffer parenchymatous and hyaline degeneration, and less commonly the intermuscular tissues present the characteristics of acute myocarditis. Acute endocarditis and inflammations of other serous surfaces are rare in typhoid fever as compared with some other infectious diseases.

Acute degeneration of the kidney and acute nephritis are quite common, and the kidney substance may present small lymphomatous foci. Similar lymphomata occur in the liver and throughout the peritoneum. Small necrotic foci are also found in the kidney and liver.

Acute lobular pneumonia and croupous pneumonia are frequent complications. Osteomyelitis is rare.

The blood in typhoid fever, unlike other infections, presents no leukocytosis, but, on the contrary, usually shows a leukopenia, the mononuclear leukocytes predominating.

Cholecystitis and gall-stones have been traced to typhoid fever. Thrombosis, particularly of the veins, has been known, and more lasting alterations in arteries, Thayer believes, may be caused by the typhoid bacillus.

Paratyphoid Fever.—This infection occasions variable lesions in the intestines. There may be simple or follicular enteritis, or ulceration of the lymph-nodes has been seen. The systemic condition is more of a bacteremia without definite localizing manifestations. It is to be differentiated from typhoid by bacteriological tests.

Tuberculosis of the intestines may be primary or secondary. It may, in rare cases, occur primarily from the drinking of infected milk



Fig. 288.—Tuberculous ulceration of the intestine.

or consumption of the meat of tuberculous animals. Primary tuberculosis of this character is most often seen in young infants. More commonly tuberculosis of the intestines is secondary to pulmonary or laryngeal tuberculosis, and is due to the swallowing of sputa.

In following the course of the tubercle bacillus in its production of intestinal tuberculosis one must remember that this organism can pass the undamaged mucosa without leaving a trace. It may settle in a submucous lymphatic, or be carried to a mesenteric gland. In the former case the primary lesion is a submucous tubercle which can extend (a) along the transverse lymphatic vessels, (b) through the muscularis to a position under the serosa, and (c) toward the mesenteric insertion and to the mesenteric gland. If no lesions occur in the gut wall, but begin in the mesenteric glands, then the lesion may extend toward the gut along the mesentery, and break out as subperitoneal tubercles which have the power to penetrate along the lymphatic vessels com-

PLATE II



Tuberculous ulceration in intestine showing miliary and infiltrative lesions beneath peritoneum and in mesentery.

municating between the submucosa and peritoneum. Tuberculous peritonitis, which usually assumes a plastic nature, may arise this way.

The usual situation of the lesions is the lower end of the ileum, and it is the lymphoid tissues that are prone to be attacked. At first the follicles or Peyer's patches become enlarged and project above the surface. Soon they undergo necrosis and discharge their contents, leaving more or less irregular caseous ulcers. The follicular ulcers are small and rounded, but the more characteristic lesion is an irregular ulcer extending transversely to the long axis of the bowel and often involving one-half or more of the entire circumference (Fig. 288).

Microscopically, the changes are found to involve the mucous membrane and the adjacent submucous coat. Early caseation is characteristic. On the serous coat may often be seen granular elevations in clusters opposite the ulcers in the mucosa, and extending in lines from the region of ulceration around the bowel toward the mesentery (Fig.



Fig. 289.—Miliary tubercles in clusters and disseminated over the serosa (peritoneum) of the intestine; the clusters are situated opposite ulcerations of the mucous membrane (modified from Bollinger).

289). These represent tuberculous lymphangitis and small miliary tubercles in the course of the subserous lymphatic vessels.

Tuberculous ulceration rarely causes perforation of the bowel, excepting in the rectum, where periproctitis and *fistula in ano* may result. The ulcers may heal, causing cicatricial distortion or stenosis. Very commonly there is associated tuberculous enlargement of the mesenteric glands, and sometimes the latter are extensively diseased, though the primary intestinal involvement is insignificant. Generalized enteritis of catarrhal character may accompany the specific ulcerative disease.

There can be hematogenous miliary tuberculosis of the gut arising as a part of the general form, as peritoneal, subperitoneal, submucosal, or interstitial tubercles.

Occasionally a hyperplastic intestinal tuberculosis occurs in which the productive tissue growth exceeds the caseation.

Syphilis is most frequent in the rectum, though cases of syphilitic disease of the small intestine or colon, in the form of localized

or diffuse gummatous involvement, sometimes with secondary ulceration, have been observed, particularly in cases of congenital syphilis.

In the rectum syphilis may appear in the form of warty elevations or as a chancre; also as mucous patches, gummatous nodules, or infiltrations. Considerable thickening of the mucosa and submucosa, with ulceration and secondary cicatrization and stenosis (*syphilitic stricture*), may result.

Anthrax occasionally affects the small intestine in persons exposed to infection by their occupations. It is met with among wool-sorters, brushmakers, tanners, and the like. More or less extensive ulceration is seen in the small intestine, and sometimes in the large intestine. The ulcers are dark colored and necrotic in appearance, and are commonly surrounded by a hemorrhagic zone. Considerable edema and hemorrhagic infiltration of the neighboring parts of the intestine may accompany the ulceration. The neighboring lymph-glands and the spleen are enlarged. The bacilli of anthrax are found in considerable numbers in the ulcers and in the surrounding tissues.

Actinomycosis of the intestines is very rare. It most commonly affects the region of the cecum, causing first infiltrations, and then ulcerations of the mucosa and submucosa.

Enteromycosis is a term applied to intestinal affections resulting from the ingestion of putrid meat, fish, sausages, and the like. Occasionally considerable epidemics may occur. The intestines may present the lesions of catarrhal enteritis or of intense croupous or pseudomembranous inflammation, and there may be erosions or ulceration. Micro-organisms of various sorts have been discovered, but no specific form is recognized. The acute general symptoms, and even the local lesions, may be caused by poisons elaborated by bacteria in tainted foods rather than by the micro-organisms themselves.

TUMORS

Connective-tissue Tumors.—Among the benign tumors of the intestines, *fibroma*, *myxoma*, and *lipoma* are occasionally met with in the submucosa as small nodular tumors or as pendulous polyps. They may occasion intestinal obstruction and even invagination.

Sarcoma of the intestine is rare. Lymphosarcomatous or lymphadenomatous enlargement of the solitary follicles or Peyer's patches may be met with in leukemia or pseudoleukemia. Round-celled sarcoma springing from the submucosa and deeper layers of the mucosa, and sometimes infiltrating the mesentery, may also occur as an independent and primary affection. Nodules of secondary sarcoma are not rarely met with in the mucosa and submucosa of the intestines (Fig. 290), and the serous covering may be studded with miliary nodules in sarcomatosis.

Epithelial Tumors.—Among the epithelial tumors may be included *inflammatory papilloma*, *adenoma*, and *carcinoma*.

Inflammatory hyperplasia of the mucous membrane may occur in association with chronic inflammations, especially in the large intes-

tine, and may lead to the formation of papillomatous or polypoid elevations of considerable magnitude.

Adenomata are more strictly of the nature of tumors, being independent of inflammatory processes, although no sharp dividing-line can be drawn between the inflammatory proliferations and the adenomata proper. The latter may occur in the form of flat elevations having a more or less uneven surface and a tendency to hemorrhage and ulceration; or in the form of papillomatous elevations of a cauliflower character. Adenomata arise by hyperplasia of the crypts of Lieberkühn in the duodenum, or of Müller's glands, and in their structure they present typical glandular acini, the tubules having a basement-membrane lined with cylindrical epithelium. Adenomata are most frequent in the



Fig. 290.—Nodule of secondary sarcoma in the mucosa of the intestine (Kast and Rumpel).

rectum, but may occur in other parts of the large intestine and in the duodenum.

Carcinoma is the most frequent tumor of the intestines. It occurs in the duodenum, especially at the papilla of the common bile-duct (Fig. 291); at the ileocecal valve, at the flexures of the colon, and in the upper or lower part of the rectum. The appearance is that of a soft, irregular, often ulcerated and bleeding elevation, projecting into the lumen of the gut and causing considerable narrowing, or surrounding the bowel by circular involvement of the entire circumference. The carcinomata of the bowel are, for the most part, cylindrical epitheliomata (Fig. 292) or glandular cancers, consisting of atypical acini and tubules, with irregular proliferation and infiltration of the neighboring tissues.



Fig. 291.—Carcinoma of papilla of Vater (Kast and Rumpel).



Fig. 292.—Cylindrical epithelioma of the intestine (Perls).

with masses of epithelial cells. Cases are met with, especially in the rectum, in which there is a clear transition of adenoma into carcinoma (adenocarcinoma), and, in general, adenomata of the bowel have a tendency to such transformation (Fig. 293). At the lower end of the rectum squamous epithelioma may occur.

The results of carcinoma of the bowel are the same as those of stenosis due to other causes, together with the consequences of the cancerous cachexia and of metastasis. Ulceration of the tumor may lead to perforation. Metastasis occurring to liver and other structures in the peritoneum is not uncommon. Outside of this cavity the secondary growths are rare. Secondary growths in the intestine are not so common.

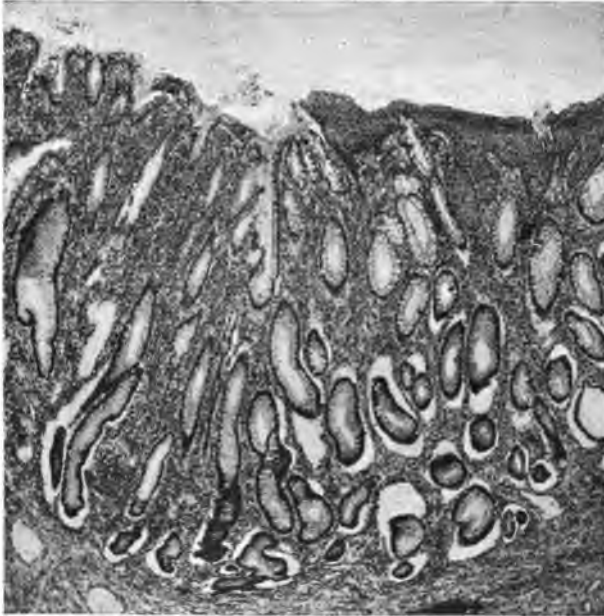


Fig. 293.—Adenocarcinoma of the rectum (adenoma destruens) (Karg and Schmorl).

They come from growths in the stomach and uterus especially. Carcinomata of the appendix are more common than previously supposed. They are of the scirrhus or simple variety and seldom cause symptoms or metastases.

Myoma of the intestines and multiple *cysts* are occasionally met with.

PARASITES

Vegetable Parasites.—Various forms of bacteria are found with such frequency in the intestinal contents that it is difficult to estimate their pathological significance. Tubercle bacilli, the bacillus of glanders and of typhoid fever, and the *Streptothrix actinomyces* produce the specific lesions of these diseases. The *Bacillus coli communis* is a con-

stant inhabitant, but probably assumes pathogenic properties and leads to inflammatory lesions when the conditions (such as irritation by coarse food, congestion, obstruction) favor its activity and multiplication. Under the same circumstances other micro-organisms likewise become active in the production of enteritis.

Animal Parasites.—The animal parasites are discussed in detail elsewhere, but may be briefly mentioned here with reference to pathological results occasioned by their presence. Various forms of protozoa have been found, and may occasion inflammation when in considerable numbers. Coccidial psorospermia occur in the epithelium of the villi of the small intestine, and the *Lamblia intestinalis* may be found attached to the epithelium. The dysentery amebæ may lie free in the contents, or may be found in the tissues, especially in the vicinity of ulcerations. They inhabit the large intestine, and are the cause of a certain kind of dysentery.

The larger intestinal parasites are, for the most part, species of Vermes. Among the tapeworms, *Tænia saginata*, *T. solium*, and *Di-bothriocephalus latus* are the most frequent. Occasionally these may lead to intestinal obstruction by forming thick knots or coils, and sometimes the head of the worm may be attached in the mouth of the bile-duct, causing obstruction and jaundice. Inflammatory changes are rarely met with as a result of these worms.

Among the nematodes, or round-worms, the *Ascaris lumbricoides*, or ordinary round-worm, is the most frequent. It is usually multiple, and may occasion obstruction of the intestine or inflammation. Sometimes it perforates the intestinal wall, but it is improbable that the perforation is due entirely to the action of the worm. Previous intestinal ulceration is the more important condition. Obstruction of the bile-ducts or of the appendix may occasionally be due to lumbricoids. The *Ankylostomum duodenale* may cause petechial hemorrhages and inflammatory disturbances in the duodenum or jejunum. The worms attach themselves firmly to the mucous surface and may be present in large numbers. The *Oxyuris vermicularis*, or thread-worm, occupies the large bowel, multiplying in the cecum and descending in the mature state to the rectum; it may occasion considerable proctitis. In female children vaginitis sometimes results from migration of the worms. The *Trichinella spiralis* when ingested in large numbers occasions violent gastro-enteritis, and its embryos perforate the wall of the intestine and migrate to the muscles.

Larvæ of various forms of flies occasionally occupy the intestinal tract, and owe their presence to the ingestion of the eggs with food. They may occasion enteritis, and may be found in immense numbers in the bowel or the stools.

INTESTINAL RUPTURE AND FOREIGN BODIES

Rupture may be due directly to traumatism or penetrating wounds; but more frequently results from ulcerations within. Duodenal (peptic)

ulcers not infrequently perforate, and typhoid ulcers occasionally cause rupture. Tuberculous, dysenteric, and other ulcers are less prone to penetrate completely. The appendix may rupture from obstruction at its mouth and secondary catarrhal, necrotic, or gangrenous inflammation of its walls. Rectal ulcers frequently cause painful diarrhea, proctitis, periproctitis, and fistulæ.

Intestinal rupture usually leads to rapid peritonitis, but occasionally recovery ensues. A localized peritonitis, by walling off the infected area, may prevent general infection. The rupture may take place between adherent coils, causing spontaneous intestinal anastomosis.

Foreign Bodies.—Various bodies that have been swallowed may lodge in the intestines. Occasionally fecal concretions or *enteroliths* are found, especially in the appendix. These consist of a nucleus of epithelial cells, mucus, hair, and the like, surrounded by inspissated fecal matter and earthy salts, particularly phosphate of lime and carbonate of calcium. They may cause considerable irritation, especially in the appendix, and even perforation.

Intestinal sand is a collection of fine particles of inorganic matter with a little organic matter. Certain foods, like bananas, favor its development.

THE LIVER

Anatomical Considerations.—The liver is peculiar in having a double circulation: one system of vessels, the portal vein and its ultimate subdivisions, receiving the blood from the digestive tract for functional purposes; the other system, the hepatic artery and its branches, supplying the nutritive blood for the walls of the blood-vessels and for the interlobular connective tissues, as well as to a certain extent the proper hepatic structure itself. The portal capillaries ramify through the acini and empty into small branches of the hepatic vein lying in the center of the acini. The capillaries of the hepatic artery traverse the interlobular tissue and ultimately empty into the interlobular branches of the hepatic vein. The primary biliary capillaries are merely spaces between the hepatic cells, the larger formed capillaries occupying the interlobular tissues.

MALFORMATIONS AND CHANGES OF POSITION

Congenital malformations are uncommon. There may be *complete absence of the organ*, especially in certain monstrosities; more frequently *adventitious hepatic tissue* is found in the suspensory ligament or elsewhere. Minor abnormalities in the lobes or fissures are more frequent. *Absence of the gall-bladder and congenital stenosis or occlusion of the hepatic ducts* are occasionally met with.

Congenital Alterations of Position.—The liver may occupy the left side in transposition of the viscera. More rarely it is displaced downward or occupies other abnormal positions.

Acquired Changes of Form.—The most important of these is contraction and lengthening of the organ by lacing. This gives rise to com-

pression along the line of the lower margin of the ribs; the right lobe of the liver may thus be divided into an upper and a lower portion by a deep fissure. The capsule is frequently thickened and the superficial acini atrophic at the line of constriction (Fig. 294). Similar indentation by the ribs posteriorly, or by the right crus of the diaphragm, results from pulmonary affections and enlargements of the liver. Other changes of form, due to special diseases of the liver, will be discussed below.

Acquired Changes of Position.—Downward displacement may result from pleural effusion or emphysema; or it may be due to relaxation and lengthening of the suspensory ligaments. The latter form is



Fig. 294.—Corset liver (from a specimen in the collection of Dr. Allen J. Smith).

more common in women than in men, and is often part of a general visceroptosis. Tight lacing may be a cause of importance. Displacement to the right or left, or tilting upward of the lower edge, may occur in association with various abdominal and thoracic affections.

CIRCULATORY DISTURBANCES

Anemia of the liver may be part of a general anemia, or it may be due to pressure upon the organ, to various diseases of the liver substance, or to compression of the blood-vessels. The substance becomes pale and, if the anemia persists, undergoes degeneration.

Active hyperemia is physiological during digestion, and occurs in association with various inflammatory abdominal diseases. It is rarely extensive, and does not lead to marked pathological changes.

Passive hyperemia results from obstruction to the circulation due to cardiac or pulmonary diseases, to pleural effusion or adhesions, or to thrombosis or compression of the upper part of the inferior vena cava.

It is especially characteristic of cardiac affections, the sluggish venous circulation of the liver accounting for the fact that this organ first evidences failing cardiac power.

The liver increases in size, often considerably; the edges are rounded, and the color on the surface is darker than normal. On section, there may be seen deeply congested central veins surrounded by lighter areas, representing the substance of the acini. If the process has persisted, secondary fatty degeneration of the peripheral zones of the acini or atrophy of these takes place, and the light color of such portions, contrasting strongly with the dark, congested central vein, suggests the name



Fig. 295.—Nutmeg-liver: chronic congestion due to cardiac disease (Bollinger).

nutmeg-liver (Fig. 295). In some instances of intense congestion small hemorrhages may occur, especially in the portions lying beneath the capsule. In the later stages degeneration and reduction of size may take place and the organ may become dark red from deposit of haematogenous pigment. To this form the term *red atrophy* is sometimes given. In other instances hyperplasia of the connective tissues between the lobules and acini occurs, while at the same time the organ is darkly pigmented. The term *cyanotic induration* may appropriately be given to such. Cases of this sort are, in reality, instances of *secondary cirrhosis*.

Passive congestion of the liver may occasion considerable disturbance of the hepatic function. The most striking evidence of this is

jaundice. This is probably due to the compression of the smaller biliary ducts and capillaries, and in part to swelling of the lining cells of these channels. The bile at the same time is probably thicker than normal, and does not, therefore, as readily escape through the ducts as in health. Microscopically, one sees fatty degeneration of the liver-cells with pigmentation within and between them, and large liver-cells with large or reduplicated nuclei as evidences of attempt at repair. The capillaries are distended with blood, the liver columns separated, and probably hemorrhagic necroses about the central veins occur, although a chronic passive congestion may exist for some time without necroses. Oertel describes a general acute necrosis of the liver due to hyperemia associated with jaundice and intoxication. The necrosis begins in the center of the acini, outside of which soon appear a fat infiltration and bile-pigment deposit. There is no stagnation of bile in the capillaries between the lobules.

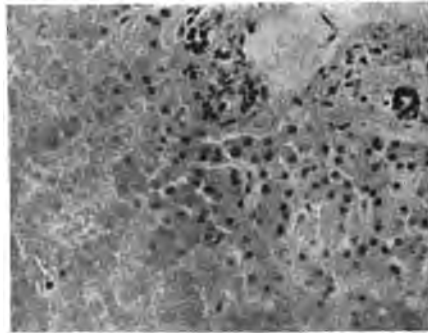


Fig. 296.—Coagulation necrosis of the hepatic cells in a case of puerperal eclampsia (Karg and Schmorl).

Embolism and thrombosis of the portal vein may occur in consequence of various diseases of the gastro-intestinal tract, particularly in cases of ulcerative enteritis. Embolic occlusion of one of the larger branches of the portal vein may occasion no serious circulatory disturbances on account of the free collateral circulation, and from the fact that the hepatic artery is capable of supplying the entire hepatic circulation. Embolic or thrombotic occlusion of the branches of the hepatic artery is similarly devoid of serious disturbance of the circulation, although a wedge-shaped hemorrhagic infarct, like a lung infarct, arises; but no degeneration is apt to follow unless the portal system for the same liver section is also damaged.

Obstruction of the interlobular branches of the portal vein, and particularly when several are coincidentally occluded, may occasion decided nutritive disturbances in the hepatic acini. Small areas of necrosis having a grayish or yellowish and somewhat granular appearance, or in other cases foci of necrosis with hemorrhagic infiltration, are the striking lesions. Such conditions are observed in most instances of death from puerperal eclampsia in consequence of toxemic thrombosis

or of embolism of placental cells (Fig. 296), and in consequence of various intoxications or infections having their origin in the distribution of the portal circulation. The immediate cause of the lesions in the latter condition is hyaline thrombosis of the interlobular portal vessels.

Thrombosis of the portal vein is most frequently the result of infective inflammation of the vein (pylephlebitis), resulting from ulcerative enteritis, appendicitis, or similar processes involving the parts from which the portal blood is received. There may be a gradual ascending inflammation and thrombosis extending from the primary focus of disease to the portal vein; or the latter may be involved in a more direct manner by infectious embolism. The portal vein and its branches in the liver become more or less obstructed, and serious disease of the liver may occur (multiple abscesses). At the same time the obstruction of the vein occasions intense passive hyperemia of the peritoneum, and ascites results.

ATROPHY AND DEGENERATIONS

Atrophy of the liver occurs in cases of death from senility, inanition, or from various organic diseases. (Pressure-atrophy has been referred to above. Acute yellow atrophy is described below.)

The greater part of the liver structure may be affected, or the atrophy may be confined to the edges or other limited portions. The liver is more or less uneven, and may at the same time be somewhat pigmented. Microscopically, the liver-cells are decreased in size, granular, and dark colored. At times the acini may disappear entirely, and reactive hyperplasia of the stroma and even proliferation of biliary ducts may ensue.

Localized atrophy occurs in the vicinity of tumors, in the acini surrounded by hyperplastic connective tissue in cirrhosis, and in parts of the liver otherwise subjected to pressure. The liver-cells of the affected part become distorted and decreased in size, and are deeply pigmented (see Fig. 312). In the later stages they break down completely and are removed. *Red atrophy* (see Congestion of the Liver) is a form of pressure-atrophy with pigmentation, the compression of the hepatic cells being due to overdistention of the hepatic veins and capillaries.

Pigmentation of the liver is prone to occur on account of the sluggish circulation through that organ, and may be of various kinds:

1. Hematogenous pigmentation (hemachromatosis) in the portal areas. Particles of altered blood-pigment are often deposited in the interlobular tissues, especially in Kupffer's stellate cells, or in the peripheral zones of the acini in cases of abnormal blood obstruction in the portal circulation. This is particularly common in pernicious anemia. In this disease the peripheral zones of the acini are habitually infiltrated with pigment matter, which responds to tests for iron, such as with ammonium sulphid or ferrocyanid of potassium and hydrochloric acid. Somewhat similar pigmentation of the liver may occur in cases of absorption of hemorrhagic effusions in the peritoneum, or in conse-

quence of other forms of blood destruction. Analogous pigmentation is often met with in the livers and other abdominal organs of drunkards. In the slate-colored liver of chronic malaria pigment is found along sinusoids, especially in Kupffer's cells. This is thought to come from the destroyed plasmodia and from disintegrated red blood-cells.

2. Hematogenous pigmentation of the central portions of the acini has been noted in connection with a red atrophy of the liver consequent upon congestion.

3. Biliary pigmentation results from obstruction of the biliary ducts, and is constantly met with in certain forms of cirrhosis and in the vicinity of new growths which compress the biliary passages. In jaundice, bile-pigments are found within liver-cells and in the supporting tissue.

4. Very rarely anthracotic pigmentation has been observed. In one case, at least, there was associated cirrhosis.

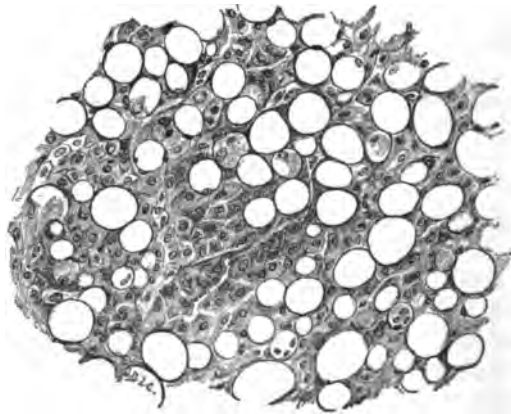


Fig. 297.—Fatty infiltration of the liver.

Fatty infiltration is more or less physiological, especially in children and in overfed individuals. Pathologically, there may be diffuse infiltration or deposit in the liver-cells of all parts of the organ. Such pathological fatty liver may result from overeating and general obesity, or may be due to pulmonary disease or anemic and cachectic conditions. It has generally been held that the immediate cause is retarded oxidation, in consequence of which fat accumulates. It is probable, however, that there is some disease of the hepatic cells, rendering them more active in storing, or less active in disposing of, fats. This seems especially true in certain cases due to poisons which cause a deposit of fat in the liver, as in geese pampered by antimonial poisoning.

The liver increases in size, often considerably; its edges are rounded, its consistency is doughy, and the color is rather yellowish and glistening. On section, there may be visible exudation of oil-drops and the knife may be covered with droplets.

Microscopically, the process is found to begin in the peripheral

portions of the acini in the form of droplets within the hepatic cells. Soon these increase in size by confluence, adjacent cells are involved, and the entire acinus eventually becomes affected (Fig. 297). In extreme cases the hepatic cell is filled with a single large oil-drop, which compresses the protoplasm and nucleus. The blood-vessels and other structures may be completely hidden from view; and the pressure of the fatty deposit may be sufficient to produce a certain degree of anemia, though not enough to occasion serious circulatory disturbances. The functional activity of the liver is diminished.

Parenchymatous degeneration, or cloudy swelling, occurs in various infectious fevers and in consequence of intoxications, notably by phosphorus, arsenic, and antimony. The liver is somewhat enlarged, and of an opaque, grayish-yellow appearance, the outlines of the lobules being extinguished. Microscopically, the liver-cells are found filled with fine albuminous granules more or less obscuring the nucleus. In most instances cloudy swelling terminates by return to the normal state; but if the intoxication or infection is continued, fatty degeneration may result.

Fatty degeneration may occur as the result of severe anemia, particularly pernicious anemia, or following cloudy swelling, as the result of infectious diseases or of intoxications. Among the infections, pyemia, yellow fever, relapsing fever, and erysipelas are notable examples. The liver may be greatly decreased in size and softer than normal; the substance not rarely is friable. The color is yellowish and oil-drops may exude from the surface. Microscopically, the hepatic cells are filled with small granular particles or droplets of fat, and in the advanced stages they break down completely into granular detritus. The nucleus is not pushed aside, but may show fragmentation of the chromatin. The liver-cells may contain single large drops of fat practically indistinguishable from those seen in fatty infiltration. The distinction of the two conditions may be exceedingly difficult. Fatty degeneration of localized areas of the liver or of individual acini or cells occurs in association with chronic hepatitis or other diseases causing pressure upon the acini.

Acute Yellow Atrophy.—The most advanced fatty degeneration of the liver occurs in the affection of the organ termed *acute yellow atrophy*. This condition is most frequent in young women, and especially in those addicted to the excessive use of alcohol. Occasionally syphilis seems the etiological factor, and in acute phosphorus- and late chloroform-poisoning the appearance of the liver is the same as that which is recognized as acute yellow atrophy. Whipple's work would indicate that chloroform destroys the fat-splitting ferment of liver-cells. Finally, some cases are idiopathic, arising without recognizable cause, which are now attributed to autogenous poisons from the intestinal or genital tract. Parturition seems a determining cause in some cases. Micro-organisms of various kinds have been found, and it is likely that all cases are toxic or infectious.

Pathological Anatomy.—The liver is decreased in size and becomes remarkably soft and friable. On section, there is found a variegated appearance, the prevailing color being a brownish or grayish yellow,

in which are scattered bright or dark red areas. The yellowish areas represent the degenerated and pigmented hepatic cells; the reddish areas, foci of hemorrhagic infiltration or pigmentation. When the hemorrhagic manifestations dominate the field the term "red atrophy" is

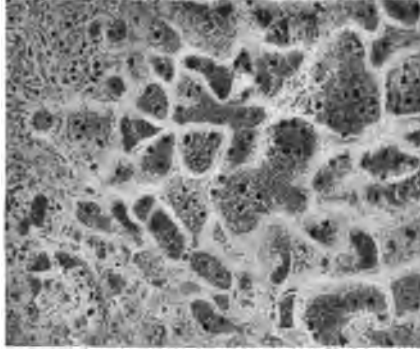


Fig. 298.—Acute yellow atrophy of the liver, showing extensive fatty degeneration and in places complete destruction of the liver-cells (Kast and Rumpel).

given. The process usually begins in the left lobe, but rapidly involves the entire organ. Sometimes the liver is increased in size during the initial stages, and occasionally a liver enlarged by previous disease suffers terminal acute atrophy.



Fig. 299.—Acute yellow atrophy of the liver from a case occurring during pregnancy.

Microscopically, the hepatic cells are found to have undergone rapid fatty degeneration or necrosis, and are filled with or replaced by yellowish pigment particles. The fat seems to be both in protoplasm and nucleus. At times there seems to be attempts at regeneration of

the liver-cells. Interstitial round cell increase is noted. As the process advances the cells are completely destroyed (Fig. 298). In the red areas referred to infiltration with blood-cells and hematogenous pigmentation are observed. In the liver of pregnancy degenerations begin in the central and midlobular regions (Fig. 299).

Associated Conditions.—Acute yellow atrophy leads to intense cholemia, in consequence of which biliary pigmentation of the various structures of the body may develop. Petechial hemorrhages may occur in the mucous or serous membranes or in the skin. The urine contains leucin and tyrosin. More or less profound acid intoxication may occur. (See Acid Intoxication, Part I.)

Amyloid infiltration occurs in consequence of syphilis, tuberculosis, and suppurative diseases of the bones, or as a result of long standing cachexia. It is habitually associated with amyloid disease of the spleen, and often of the kidneys and other structures.

Amyloid infiltration begins in the smallest blood-vessels between and within the acini, causing a more or less pronounced thickening of their walls. The liver-cells themselves may be secondarily involved, but more frequently undergo atrophy and fatty degeneration in consequence of the pressure and of diminished nutrition due to compression of the blood-vessels (Fig. 300).

The liver is enlarged, denser than normal, its edges rounded, and the tightly drawn capsule is smooth and glistening. Not rarely it presents a striking translucency, and on section the color is grayish white or yellow. The peripheral and central zones of the acini are sometimes readily distinguished by their light color from the innermost portions, which are least affected.

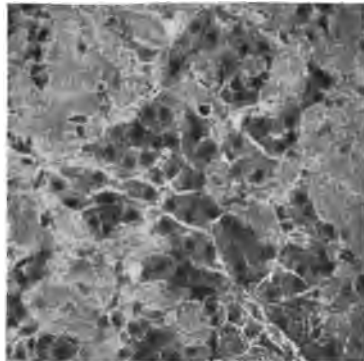


Fig. 300.—Amyloid liver (from a photograph by Dr. Wm. M. Gray).

Dropsical infiltration of the liver-cells occurs in cases of intense infection and intoxication, especially such as originate in some part of the portal circulation. It is found particularly in the vicinity of necrotic areas due to embolic occlusion of the interlobular portal veins. The liver substance is swollen, and, microscopically, the cells are cloudy and oftentimes vacuolated. The cells and columns are pushed apart by the fluid.

Necroses of the liver occur as large areas or in small foci. They are found in infections and intoxications, the former causing focal, the latter massive, lesions. The pathological alteration is coagulative. The focal necroses of typhoid fever, septicemia, and the like are small opaque, yellowish-gray, ill-outlined dots in the parenchyma, giving the microscopical appearance as outlined under Necrosis (*q. v.*).

INFLAMMATIONS

Hepatitis, or inflammation of the liver, may be of several forms: a parenchymatous, an acute interstitial, or a chronic interstitial.

Parenchymatous Hepatitis.—In the course of various infections and intoxications a certain amount of parenchymatous degeneration of the liver-cells may take place. This was formerly described under the name “parenchymatous hepatitis.” The term is generally inappropriate, though in some instances there is associated with the degeneration of the hepatic cells a certain amount of cellular infiltration and reactive inflammation. To such cases the term “parenchymatous inflammation” might be applied, though, in reality, even these are more degenerative than inflammatory in nature. To the combination the term “acute diffuse hepatitis” may be applied. The lesion is commoner in the general infections of the lower animals than in man. It is sometimes impossible to say which structure, parenchyma or its support, is affected most.

Acute Interstitial Hepatitis and Abscess of the Liver.—Bacteria may gain access in several ways. In some cases penetrating wounds, or perforation of gastric or duodenal ulcers or of other pathological lesions into the liver, occasion direct infection. In other cases the micro-organisms are carried in the circulation and enter the liver with the portal or hepatic blood, or by retrograde embolism through the hepatic veins from the vena cava. Finally, infection may occur by invasion of the bacteria along the bile-ducts.

Most frequently hepatic abscess is secondary to ulcerative disease of the intestines, notably dysentery. In this disease the specific amebæ are carried to the liver in the portal circulation, and occasion necrotic foci in which the bacteria carried with the amebæ multiply and give rise to the further changes constituting an abscess. Similar embolic abscesses occasionally follow appendicitis and perityphlitis, or various forms of intestinal ulceration. Thrombophlebitis of the portal vein not rarely extends to the smaller branches within the liver, and occasions multiple suppurative foci.

In cases of general pyemia multiple abscesses of the liver may occur, especially when the primary infection occurs within the abdomen. Infection by invasion along the biliary tract is especially prone to occur when there is obstruction of the bile-ducts by calculi or otherwise. In tropical countries traumatism without visible contusion may lead to abscesses, and it is not unlikely that micro-organisms from the biliary passages penetrate the hepatic structure in the injured portions.

Among the micro-organisms that have been discovered are the streptococci and staphylococci, the *Bacillus coli communis*, and others less frequently.

Pathological Anatomy.—Dysenteric and traumatic abscesses are usually solitary, and generally occupy the right lobe. In the early stages they appear as spots of grayish or yellowish color, in which the division of the lobules is lost and which assume a more and more granular ap-

pearance. Subsequently softening takes place and a cavity is formed. This increases in size until, in advanced cases, it may reach enormous proportions. The contents consist of curdy or creamy pus having a yellowish, brownish, or often quite reddish appearance, and the wall is composed of an ill-formed pyogenic membrane. The abscess may consist of a single cavity or may be partially lobulated. Sometimes there are multiple abscesses. If the cavity is small, resorption of the pus may take place and a cicatrix may result. In other cases inspissation and encapsulation ensue. Large abscesses may rupture into the pleura, into the stomach or intestines, into the peritoneal cavity, or externally.

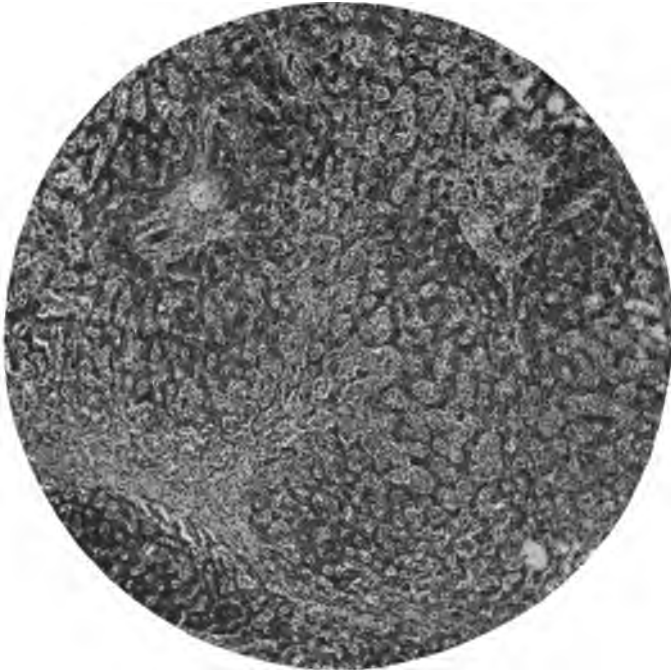


Fig. 301.—Cirrhosis of liver due to chronic passive congestion.

Not rarely the diaphragm and lungs are penetrated, and the pus is evacuated through the bronchi.

Metastatic abscesses, and those due to infection from the biliary ducts or to suppurative pylephlebitis, are multiple and usually of small size.

Chronic Interstitial Hepatitis or Cirrhosis of the Liver.—These terms are applied to a group of affections characterized by more or less diffuse hyperplasia of the connective tissue of the liver, usually most pronounced in the interlobular tissues and surrounding the branches of the portal vein, but sometimes invading the lobules themselves. Secondary atrophy or, less commonly, certain atypical forms of hyperplasia of the liver-cells follow after the connective-tissue hyperplasia.

In some instances the capsule of the liver is also involved in the fibrous overgrowth.

The *etiology* of cirrhosis is still in many respects obscure. The irritants, toxic agents or bacteria, may reach the liver through the portal vein, the hepatic artery, the biliary channels, and possibly via the lymphatics or the peritoneal covering of the organ. The most important routes are the portal vein and the bile-ducts, as either of these furnishes a possible path for the entrance of the many forms of micro-organisms that may occupy the intestinal tract; the portal vein in particular may convey poisons ingested or manufactured in the stomach or intestines. The occurrence of cirrhosis following certain general infections (scarlatina, malaria, syphilis) suggests the possibility that the causative agents may enter through the hepatic artery—that is, from the systemic arterial blood.



Fig. 302.—Atrophic cirrhosis of the liver (Laennec type).

A form of hepatic fibrosis that, pathologically speaking, may be regarded as chronic interstitial hepatitis is that which follows long-standing congestion of the liver in cases of cardiac disease, emphysema of the lungs, and other causes of stasis in the inferior vena cava. The terms *cirrhosis from passive congestion* and *cardiac cirrhosis* are sometimes used. In this condition the central veins of the lobules are over-distended, and pressure-necrosis of the surrounding liver-cells followed by endothelial hyperplasia and intralobular fibrosis are later developments. The cross-section of the liver shows a variegated appearance, due to the dark (congested) central zone of the lobules and the lighter colored periphery. The term *nutmeg-liver* indicates this stage. Finally, the fibrosis becomes more extensive, and the whole organ is more or less deeply stained with blood-pigment (*red atrophy* or *induration*).

Localized areas of fibrosis may occur in the liver, as in any organ around tumors, granulomatous processes, or any pathological area.

Varieties of Cirrhosis.—Two types of cirrhosis, sufficiently distinctive in their pathological and clinical features to be regarded as separate entities, are the *portal* and the *biliary*. The older terms, *atrophic* and *hypertrophic*, are falling into disuse as less distinctive. A portal cirrhosis may be atrophic or hypertrophic, and a biliary cirrhosis is not of necessity hypertrophic.

Portal Cirrhosis.—Gin-drinker's liver, Laennec's cirrhosis, is an interlobular increase of connective tissue causing compression of lobules and portal radicles (Fig. 302). It is the commonest form of cirrhosis of the liver, and has been ascribed to excessive use of spirits, especially raw.

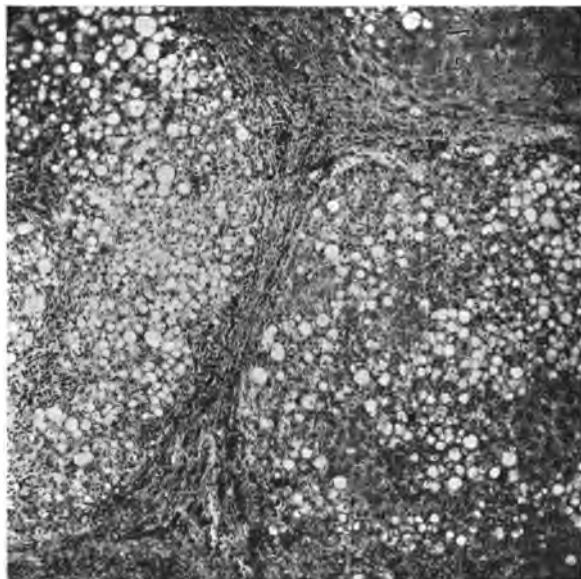


Fig. 303.—Fatty alcoholic cirrhosis.

There seems to be small doubt that sedentary life, gastro-intestinal disorders, and alcohol predispose to this form; an opinion not at all inconsistent with the present idea of its immediate causation. It is generally ascribed today to toxic agents passing in through the portal vein, causing necrosis of the adjacent liver-cells, a round-cell infiltration about the radicles of the portal vein, fatty metamorphosis, connective-tissue overgrowth, and secondary contraction. This affects the nutrition of the liver parenchyma, favors continuance of degeneration, and so squeezes the softer tissue that a roughening of the surface results (*hob-nail liver*).

It has been suggested that the colon bacillus may be a factor in the causation of portal cirrhosis, since it will induce fibrosis when gaining access to a liver already the seat of necrosis or fatty change, a theory

fairly well supported by experimental evidence. Chronic gastro-intestinal disease, often a forerunner of cirrhosis, gives ample opportunity for focal or diffuse loss of resistance in the liver, because considerable amounts of toxic substances are formed and so pass through this organ in the portal circulation. The constant use of alcohol, a habit undoubtedly favoring cirrhosis, supplies an easily oxidizable substance to the liver, and food fat, not so easily burned, is stored, thus acting as a great burden for the cell, so that bacterial infection is met with no resistance, the cell succumbs, and fibrosis follows (Fig. 303). The older idea that alcohol acts as a direct irritant to the hepatic cells and by destroying these initiates the cirrhotic process cannot as yet be thrown aside.

Morbid Anatomy.—In the earliest stages the liver is often enlarged, but in the typical advanced form it is contracted, extremely hard,



Fig. 304.—Atrophic cirrhosis of the liver of a boy aged sixteen years, showing also thickening of the capsule and ligaments (perihepatitis).

granular or irregularly uneven on the surface, and, on section, resistant to the knife (Fig. 304). The size of the liver, even in advanced stages, is by no means always small. A study of statistics obtained at the post-mortem table shows that the liver in perhaps a majority of the cases of otherwise typical Laennec's cirrhosis is larger than the normal organ. This is due to fatty infiltration of the liver-cells, to associated congestion, or to an attempt at replacement of lost parenchyma by hypertrophy or hyperplasia. This attempt is transient and ineffectual. The highly fatty cirrhosis of the interlobular type gives a liver of egg-yolk color. The surface of section presents bands of connective tissue surrounding groups of acini, and compressing them so that they rise above the surface. The connective-tissue bands are dull gray or white in appearance, the enclosed acini yellowish or brownish.

The growth of connective tissue follows its usual course of excess, and is shortly found as wide, irregular bands, rather poor in cells, separating the lobules ("unilobular"). It may instead embrace a group of lobules, giving rise to the so-called "multilobular cirrhosis."

Microscopically, cirrhosis is characterized by a proliferation of the connective tissues around the interlobular branches of the portal vein. In the earlier stage this occurs in the form of round-cell infiltration and proliferation of fibroblastic cells, causing moderate obstruction to the portal circulation. Later, the connective tissue becomes sclerotic, greater compression of the portal veins ensues, and considerable obstruction of the circulation results. At the same time the acini are compressed and suffer degeneration and atrophy. The atrophic lobules, with their degenerated and pigmented liver-cells, may be a striking feature in the histological picture. There is little tendency to extensive

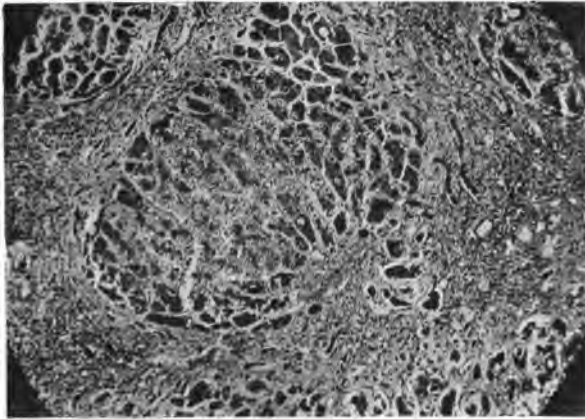


Fig. 305.—Cirrhosis of the liver, showing a lobule in the center surrounded by dense connective tissue. The hepatic cells within the lobule are extensively degenerated (fatty), and those at the periphery deeply pigmented.

invasion of the acini themselves by the inflammatory process. New-formed biliary ducts may be present in considerable numbers in the hyperplastic interlobular tissue.

Associated Changes.—The marked result of atrophic cirrhosis is obstruction to the portal circulation. This occasions congestion of the spleen and gastro-intestinal mucosa and, eventually, ascites. When the obstruction becomes extreme, collateral circulation may relieve the congestion of the portal system. The most prominent anastomoses are those between the gastric and esophageal veins, and between the hemorrhoidal veins and the veins of Retzius with the retroperitoneal veins. The veins of the round ligament increase in size and may communicate with the superficial veins at the umbilicus (*caput medusæ*).

Gastro-intestinal catarrh and enlargement of the spleen are usually prominent in cirrhosis. Jaundice is rare, because the bile-ducts are rarely compressed. There may be a low-grade cirrhosis of the pancreas.

In some instances the liver is large and smoother, softer and lighter in color, from the fact that considerable fatty infiltration of the acini is associated with the cirrhosis (fatty cirrhosis, Figs. 303 and 305). This is the so-called "beer-drinker's liver." In one case, in a small man seen by one of the authors, the organ weighed 9½ pounds. In the later stages such cases may become converted into the typical form by absorption of the fat.

Pathological Physiology.—Cirrhosis of the liver occasions gastrointestinal symptoms by obstructing the portal circulation, and probably also by altering the functional action of the liver. Metabolic disorders of some sort also result from the hepatic disease, but the nature



Fig. 306.—Biliary cirrhosis of liver.

of these is as yet unknown. There is often a toxic state with delirium, the exact cause of which is not understood. The fatal termination often comes in the form of sudden or gradual coma, which is probably toxic.

Biliary cirrhosis is a form accompanied by inflammatory, obstructive, and pigmentary changes in or surrounding the bile-duct system. Any one of these may dominate the pathological picture (Fig. 306).

Two types have been described: In the first, *obstructive biliary cirrhosis*, the hepatic disease follows obstructions of the biliary ducts, and is, therefore, largely of mechanical origin; in the second, *Hanot's hypertrophic cirrhosis* or *true biliary cirrhosis*, gross obstruction of the

ducts does not precede the hepatic disease. At most, catarrhal cholangitis precedes or accompanies the disease and may in part occasion the associated jaundice.

Obstructive biliary cirrhosis is a fibrous overgrowth due to back pressure upon bile channels, which causes stagnation, peribiliary congestion, liberation of irritative pigment, reactive tissue change, and fibrosis. The obstruction may be due to gall-stones, tumors, or atresia of the bile-ducts.

The appearance of the liver is much the same as that seen in hypertrophic cirrhosis of the Hanot type. The organ is uniformly enlarged, and may be somewhat granular upon the surface or entirely smooth. On section, the substance is found to be deeply bile stained, and has a yellowish or greenish color. The substance is firm, and the overgrowth of connective tissue may be visible on the surface. Bile-ducts, distended and irregular, are to be seen.

Microscopically, the first discoverable changes are areas of insular necrosis in the peripheral zones of the acini. Subsequently, proliferation of connective tissue replaces these and spreads to the interlobular tissues. Proliferation around the interlobular biliary capillaries (*peri-angiocholitis*) may be a striking characteristic from the first, and multiplication of new bile-ducts and of hepatic cells is observed. In cases of absolute obstruction of the gall-ducts, and in cases in which active chemical changes in the bile have occurred, rapid fatty degeneration and acute atrophy of the liver may be the terminal phases. The spleen is little, if at all, enlarged, and ascites does not occur until very late, if at all.

Hanot's cirrhosis is a diffuse increase in fibrous tissue following the bile-ducts and associated with inflammatory changes in and around them. The cause is generally thought to be an infection traveling up the biliary system. By reason of the association of bile-ducts in the interlobular septa with the intralobular bile radicles the infiltrative and proliferative processes invade the outer sections of the lobules and do not remain so largely interlobular as is the case in Laennec's cirrhosis.

Microscopically, proliferation in the interlobular connective tissues is found, as in the atrophic form, but it does not bear the same relation to the portal veins and is less prone to cicatricial contraction. Unlike the portal form, there is decided extension into the peripheral zones of the acini, and everywhere between the columns of hepatic cells there may be seen proliferated fibroblastic cells. This inward extension of the fibrous tissue separates and distorts segments of bile radicles and small ducts near the lobular border, giving the appearance of many newly formed bile-ducts. There is, indeed, an actual increase of bile-ducts. Their prominence on section seems due to an attempt at regeneration by peripheral parenchyma cells. All these changes are accompanied by biliary pigmentation, manifested both in the organ and generally in the body. There is no obstruction to the portal or gastric circulation, so that ascites and varices do not occur. The spleen is always enlarged and sometimes decidedly so.

Pigmentary Cirrhosis.—Certain rare forms have been ascribed to carbon, but the most important is that associated with *hemosiderosis*, due probably to excessive blood destruction, and associated with the bronzed diabetes of chronic pancreatitis. Again, in Banti's disease, with its excessive hemolysis, probably due to increased splenic activity, there is a pigment collection in the liver which may lead, in the advanced stages, to a cirrhosis.

Large scars may occur after massive destruction of liver tissue, in acute yellow atrophy, poisoning, gummata, etc. These have been called "toxic cirrhoses," but it is well to remember that they represent finished reparative processes, and do not tend to spread. Of this

nature may be the fibrosis in the vicinity of tuberculomata, which some authors have called "tuberculous cirrhosis."

Perihepatitis.—Inflammation of the capsule of the liver and of the superficial portions of the hepatic structure may be associated with cirrhosis (Fig. 307), and not rarely occurs in consequence of chronic peritonitis. It may lead to considerable thickening of the capsule. The pressure of the contracting fibrous tissue may occasion atrophy of the underlying hepatic substance, and a more or less uneven and atrophic organ results. Primary inflammation of the capsule may be an expression



Fig. 307.—Perihepatitis associated with cirrhosis of the liver.

of syphilitic infection, and may occur alone or in association with thickening of the peritoneum. Reference will be made, in the discussion of diseases of the peritoneum, to a special form of hyperplastic perihepatitis—that known as the *Zuckergussleber* of Curschmann.

Syphilitic cirrhosis is to be mentioned because of its common occurrence in congenital syphilis. The liver is large and hard, and the fibrosis is pericellular, separating not only liver columns, but the cells themselves. Gummata are usually present. Spirochetes are exceedingly numerous.

HYPERTROPHY

The regeneration after injuries of the liver shows the power of the liver-cells to undergo active multiplication. Not rarely, active hyperplasia of liver-cells, from liver-cell or bile-duct epithelium, throughout the entire organ may occur in association with other diseases, notably hypertrophic cirrhosis. A simple hypertrophy of the liver also occurs in certain well-developed, robust individuals. Enlargements of the liver formerly regarded as hypertrophies are, for the most part, due to pathological conditions.

Regeneration of healthy liver can take place when a portion has been destroyed by injury. The hypertrophic and hyperplastic cells in this case and in cirrhosis are large, sharply outlined, and take the stain more deeply. Bile-duct epithelium seems to be able to generate liver-cells.

RUPTURE OF THE LIVER

Rupture may occur from direct traumatic injury, and is particularly common in the newborn when forcible delivery has been necessary. In the latter cases small injuries with secondary hemorrhagic infiltration are observed near the surface of the organ. Portions of liver-cells may be loosened and may be carried as emboli to the lungs. The injury is repaired by active hyperplasia of the liver-cells and of the biliary capillaries, and in this manner the affected part may be restored without the development of scar tissue. Large injuries, however, occasion the formation of cicatricial tissue.

INFECTIOUS DISEASES

Tuberculosis may occur in the form of minute, translucent, miliary tubercles, which may be scarcely visible to the naked eye (Fig. 308), or in the form of larger foci. Tuberculosis of the liver is always a secondary disease. The tubercles arise in the interlobular tissue or in the acini themselves. The larger caseous tubercles are rare; they may be associated with a local or diffuse sclerotic contraction of the organ. The association of general cirrhosis and a tuberculous lesion is frequent, but probably accidental. In the immediate vicinity of a caseous mass connective-tissue overgrowth always occurs, and caseous masses may become encapsulated. Bile-duct tubercles occur along the course of these tubes, and may ulcerate into the lumen. Miliary tuberculosis of the capsule of the liver not rarely occurs in tuberculous peritonitis.



Fig. 308.—Miliary tubercles in the liver.

Syphilis is met with in the form of diffuse infiltration and cirrhosis, or in the form of gummata. Either of these varieties may be found as a result of acquired or of hereditary syphilis. In the diffuse form the liver presents much the same appearances as in atrophic cirrhosis, but as the connective-tissue bands are much more pronounced, the liver is prone to be irregularly contracted and lobulated—hepar lobatum (Fig. 309). Gummata may occur in any part of the organ, and may be single or multiple, massive or miliary, presenting themselves as rounded, yellow-

ish, or grayish areas, oftentimes showing central necrosis and surrounded by connective-tissue hyperplasia (see Fig. 119). Complete cicatrization may lead to decided scar formation. In addition to these forms, congenital syphilis may manifest itself in the form of a uniform, diffuse con-



Fig. 309.—Syphilitic cirrhosis of the liver: lobulated liver (Kast and Rumpel).

nective-tissue hyperplasia and round-cell infiltration. The liver-cells are pushed apart and are ill-developed or atrophic (Fig. 310).

Leprosy occasionally affects the liver, causing the formation of nodular masses.



Fig. 310.—Diffuse congenital syphilis of the liver.

Actinomycosis, primary or secondary, occurs in the liver as single or, more commonly, multiple abscesses with granular necrotic contents, surrounded by a productive deforming connective tissue, and tending to cause adhesions through which the process travels to adjacent structures.

TUMORS

Fibromata, lipomata, and myomata are occasionally observed as nodular masses, but have little significance.



Fig. 311.—Section through a large nodule of sarcoma of the liver, showing the practically normal liver substance above, and the sarcoma with central softening below.

Angioma is an important tumor occurring upon the surface of the organ; it is usually of small size, rarely exceeding that of a wal-

nut. It is more commonly found in persons who have died at advanced years than in young persons. Angiomata appear as dark-red or bluish, slightly elevated areas, either sharply outlined and encapsulated, or merging gradually into the surrounding tissue. Microscopically, they are found to be cavernous angiomata or cavernomata, not true tumors, and doubtless owe their origin to dilatation of the capillaries, with coincident atrophy of the liver-cells. Some are associated with hyperplasia of the vascular endothelium and belong to the hemangio-endotheliomata.

Various explanations have been given for these tumors, among the theories being developmental defect, capillary distention, and true neoplastic growth. Only those associated with endothelial change can properly be called neoplasms.



Fig. 312.—Cirrhotic cancer of the liver (Hanot and Gilbert).

Sarcoma of the liver may occasionally be primary, but is exceedingly rare (Fig. 311). Secondary sarcoma, on the other hand, is very common, especially the melanotic form following primary sarcoma of the eye.

Lymphadenomata are frequent in the liver in the course of the generalization of leukemic lymphadenoma; they are best considered as mere infiltrations of lymphocytes consequent upon the enormous leukocytosis of this disease, but they may represent, of course, hyperplasias of preëxisting lymph-cell collections.

Adenoma of the liver is met with in several forms. There may be either nodular masses, more or less encapsulated and of grayish-white or pinkish color, or a form of diffuse infiltration of the liver substance by encapsulated nodules of similar character. Considerable cirrhosis of the

liver may be associated with the latter cases, and they cannot be clearly distinguished from cirrhotic cancer (see below).

Carcinoma of the liver is rather rare as a primary tumor, but, like adenoma, may be nodular or diffuse. The *nodular* or *massive cancer* appears as a single mass of varying size, oftentimes surrounded by local metastatic nodules. On section, the color is grayish or pinkish, and there may be central necrosis and softening. *Diffuse hepatic cancer* occurs as a widespread and more or less uniformly distributed infiltrating growth. Not rarely in such cases there is associated cirrhosis, and the macroscopical appearance of the liver may be strikingly like that of an ordinary cirrhosis, though the liver is sometimes much enlarged (Fig. 312). The terms *cirrhotic cancer* and *cancer with cirrhosis* have been applied to this form. Finally, the diffuse form may surround and spring from the

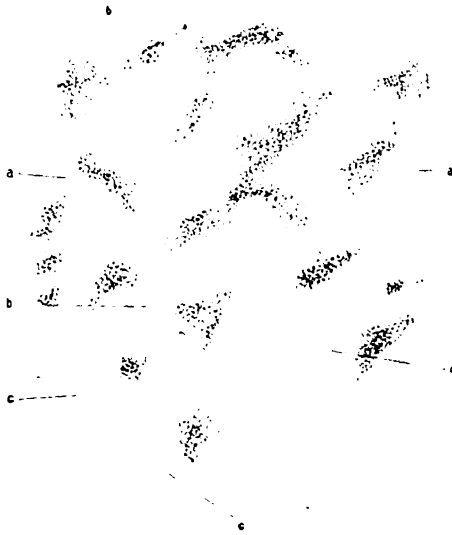


Fig. 313.—Secondary cancer of the liver: *a*, Columns of liver-cells filled with bile-pigment; *b*, endothelial walls of capillaries; *c*, carcinomatous emboli in the capillaries (Hanot and Gilbert).

periportal structures, and may ramify in the form of an interlobular infiltration. Microscopically, the cancers are simple or adenomatous.

Formation and Structure of Adenomata and Carcinomata.—Microscopically, there is no sharp dividing-line between these growths. The adenomata present tubular formations of a more or less elongated and tortuous character, composed of cylindrical or of more irregular-shaped epithelial cells. In some instances these are strikingly like new-formed biliary capillaries, and perhaps they occasionally originate from these structures. More commonly, however, the origin would seem to be from the hepatic cells themselves. The columns of hepatic cells undergo proliferative change, and at the same time become somewhat transformed, assuming the tubular arrangement of adenoma. Occasionally adenoma and cystic adenoma originate from the mucous glands of the

larger biliary ducts. When cirrhosis is associated with adenomatous

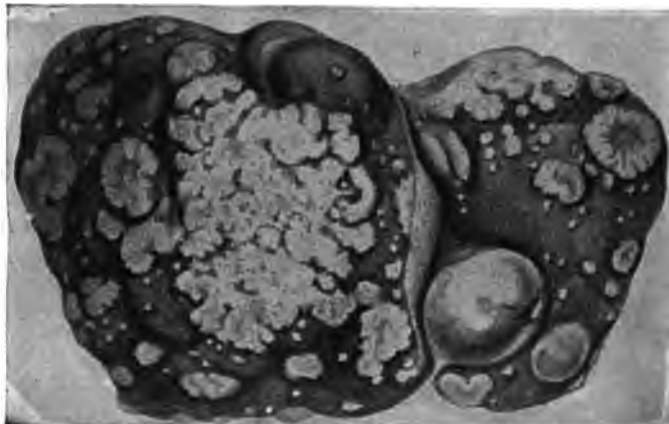


Fig. 314.—Metastatic nodules of carcinoma on the surface of the liver (Hanot and Gilbert).

proliferation it is probable that the primary change is a cirrhotic overgrowth which induces secondary hyperplasia of the epithelial cells, instead of degenerative changes, such as usually result from the pressure of new-formed fibrous tissue.

Carcinoma of the liver is similar in origin and structure to adenoma. The cellular acini and tubules are more irregular, and there is an evident tendency to diffuse infiltration and atypical formation of acini.

Secondary carcinoma of the liver is very common as a result of carcinoma of the stomach or of other parts of the portal distribution. It is usually due to cancerous embolism in the portal capillaries, with subsequent development of the emboli (Fig. 313). The liver becomes enlarged, and presents nodular masses upon its surface or within its substance. These nodules vary from the size of a pea to that of an apple, and are frequently sharply delimited by capsule formation, especially those which have reached considerable size (Fig. 315). Not rarely the nodules are indented upon the surface (umbilicated) from central softening or from contraction of fibrous tissue within (Fig. 314). Secondary



Fig. 315.—Metastasis of pyloric carcinoma in liver.

cancer of the liver may also result from direct extension of cancer of the

stomach or of the gall-bladder and biliary ducts. In all cases the new growths tend to compress the bile-ducts and lead to biliary pigmentation of the liver substance, as well as to general icterus.

Cysts of the liver are rare. They may spring from the biliary ducts which have suffered simple dilatation, or from the mucous glands of the larger bile-ducts (cystic adenoma). Occasionally small cysts are seen which suggest origin from dilatation of the lymphatic channels.

PARASITES

Of the protozoa, coccidial *psorospermia* (Fig. 316) have been occasionally demonstrated in the human liver in small nodular tumors; but a more important parasite is the *Entamæba histolytica*, occurring in abscess of the liver secondary to amebic dysentery. The pus of the abscess may

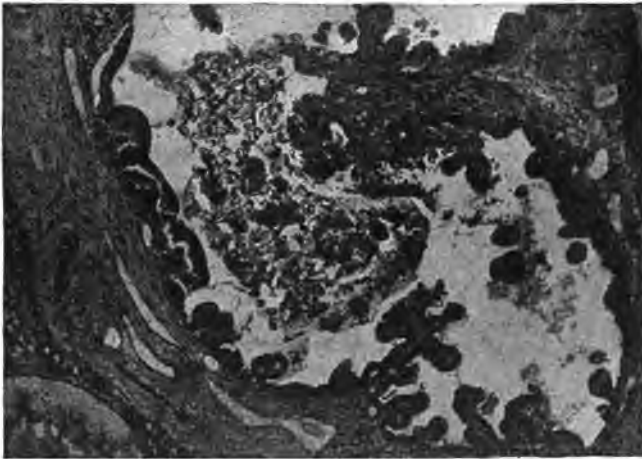


Fig. 316.—Coccidia in the wall of a bile-duct. The cut shows in the center active proliferation of the wall of the duct, with numerous ovoid coccidia massed in the tissue.

contain immense numbers of the amebæ, and doubtless these organisms bear an important relation to the lesion, perhaps causing necrosis by their own activity and then liberating pyogenic organisms which they have carried from the intestines, and which complete the pathological process. The larval *Linguatula rhinaria* is occasionally met with.

The *Fasciola hepatica* and the *Dicrocoelium lanceatum* occasionally infest the biliary ducts, and the *Schistosoma hæmatobium* the portal vein. *Ascarides* sometimes creep upward in the biliary ducts as far as the branches within the liver. The *Cysticercus cellulosæ* is a rare parasitic formation.

Echinococcus Cyst.—The most important parasitic disease of the liver is the echinococcus cyst, caused by the presence of the larvæ of the *Tænia echinococcus* (see Part I). This parasite occasions cystic formations of various kinds within the liver. The cyst has a double wall: the outer, of connective tissue; the inner, a parenchymatous membrane,

from which buds (brood-capsules) and secondary cysts are prone to originate. There may be a single cyst containing clear liquid of low specific cavity, or a mother-cyst containing daughter-cysts, either upon



Fig. 317.—*Echinococcus multilocularis* (Luschka).

the inner wall or floating free within the liquid after their separation. Sometimes even granddaughter-cysts are formed. Occasionally the daughter-cysts are found outside of the mother-cyst, extrusion in such cases having taken place. A form of multilocular cyst is more rarely observed in which there are numerous small cysts embedded in more or less firm connective tissue (Fig. 317). *Echinococcus* cysts may rupture

into the abdomen or into surrounding viscera. The most serious condition is rupture into the vena cava, as the result of which hydatid disease of the heart, the brain, or other organs may ensue. Bacterial invasion occasionally takes place, and abscess may result. Finally, the liquid contents may be absorbed, and the cyst may be reduced to a small



Fig. 318.—*Echinococcus* cyst of the liver (from a specimen in the Museum of the Philadelphia Hospital).

cavity having a shrivelled wall and containing granular or caseous detritus (Fig. 318). *Echinococcus* cysts may press upon the gall-duct, producing jaundice, or upon the portal veins, causing ascites.

THE BILIARY DUCTS AND GALL-BLADDER

INFLAMMATIONS

Cholangitis, or inflammation of the biliary ducts, is most frequently secondary to duodenal catarrh, though it may be the result of direct irritation by gall-stones, by foreign bodies which have entered from the intestine, or by parasites or bacteria. In the cases secondary to duo-

denitis the inflammation usually extends but a short distance upward from the mouth of the common bile-duct, but there may sometimes be more extensive involvement of the ducts, and the mucous membrane of the gall-bladder may be affected at the same time. The mucosa is swollen, more or less edematous, and secretes abundant mucus. The result is obstruction of the duct with retention of bile, and consequent jaundice.

Suppurative cholangitis may occur as an independent condition in consequence of certain infectious diseases, but is more commonly secondary to obstruction of the common duct or hepatic duct. Bacterial invasion from the intestine or through the blood causes decomposition of the retained bile and inflammation of the ducts. Sometimes suppurative cholangitis results from the rupture of an abscess of the liver into the bile-ducts. The association of cholangitis, simple or sup-



Fig. 319.—Purulent cholangitis, showing suppuration following the biliary tract from the hilus, and producing abscesses, one in section (from a specimen in the collection of Dr. Allen J. Smith).

purative, with typhoid fever is of considerable clinical interest. Among the micro-organisms discovered in suppurative cholangitis the pyogenic micrococci and the *Bacillus coli communis* are most frequent. The bile-ducts are filled with more or less decomposed bile or with puriform liquid, and the walls of the ducts, especially the larger ones, may present an ulcerated or necrotic appearance. Retention of bile and jaundice result early. Small dilatations may occur in places where the duct has become deeply ulcerated, and later hepatic abscesses of considerable size may form (Fig. 319).

Chronic cholangitis may be the outcome of an intense acute attack or repeated acute attacks, but is more commonly met with as a consequence of chronic obstruction of the ducts and retention of bile. A localized form, causing cicatricial stenosis, results from intense inflammatory

lesions following the passage of stones. The gall-ducts in chronic cholangitis are more or less thickened, and in the cases due to obstruction may be considerably dilated.

Results of Cholangitis.—In the acute form extension may take place to the ducts within the liver, and in case of bacterial invasion pericholangitis and abscesses may form. More commonly acute cholangitis leads to but a temporary overfilling of the biliary capillaries with bile, and, in consequence, to obstructive jaundice. When the obstruction is continued for a considerable length of time, reactive changes occur in the liver, constituting the form of cirrhosis called "biliary cirrhosis" (see p. 669).

Cholecystitis, or inflammation of the gall-bladder, may result from extension of cholangitis, or may be due to the irritation of retained bile or of gall-stones. If it should be primary, the communicating bile-ducts are soon involved. It is a fairly common sequel of typhoid fever, and the typhoid bacillus has been found in the contents of the gall-bladder, sometimes a considerable time after the original infection had subsided. In this subacute or chronic typhoid cholecystitis and in similar conditions there is a mild hypertrophic catarrh. This permits the bacteria to hide in the depths of the membrane more securely. The epithelium is often loosened or set free, and with the abundant mucus forms a nucleus for gall-stones. The acute inflammation is prone to assume a purulent character, and the gall-bladder may become filled with pus (*empyema of the gall-bladder*). This may rupture, discharging into the abdominal cavity, into adjacent viscera, or externally. The wall of the gall-bladder is usually much thickened and the mucous membrane is swollen and ulcerated. The dependent position of the sac favors retention of exudate and involvement of the serous coat, which may eventually lead to adhesions with adjacent organs if the infection be not of a kind to cause rapid suppuration. If, however, the condition be actively suppurative, fistulous tracts may be established with other viscera. If bile escape into the peritoneum, inflammation and necrosis arise. The results of long-continued non-suppurative cholecystitis are either distention by complete blocking of the outlet and retention of the contents when the mucosa continues to produce an exudate, or an atrophic fibrosing change in the wall, whereby the organ shrivels.

STENOSIS AND DILATATION

Stenosis of the bile-ducts is most commonly the result of acute inflammation, causing thickening of the mucosa and accumulation of mucus. It may result from chronic cholangitis with cicatricial overgrowth of connective tissue; from the impaction of gall-stones, or the presence of various foreign bodies, such as particles of food, mucus, round-worms or other parasites within the duct; from pressure by aneurysms, by tumors of the head of the pancreas, pylorus, duodenum, lymphatic glands, or of the liver; and from tumors of the gall-ducts themselves. Sometimes it is due to the constriction of adhesions result-

ing from peritonitis. Obstruction of the ducts leads to the retention of bile and dilatation of the ducts above, with consequent enlargement of the liver and jaundice. Obstruction of the cystic duct, which is most frequently due to the impaction of a stone, may occasion dilatation of the gall-bladder with dropsical liquid, in consequence of the passive hyperemia produced by compression of the veins at the neck of the gall-bladder. This condition is spoken of as *dropsy of the gall-bladder*. Sometimes suppurative inflammation occurs, and empyema of the gall-bladder results.

Congenital atresia of the gall-passages is a rare condition ascribed to antenatal interlobular cirrhosis, due to toxins entering through the



Fig. 320.—Suppurative pylephlebitis, showing infiltration around the bile-ducts and, in places, as at (a), a breaking down of the duct and the surrounding tissue to form necrotic abscess cavities.

placenta. It gives the changes mentioned above and causes death in the first year.

Contraction of the gall-bladder, or even complete shrinkage or atrophy, may result from obstruction at the mouth of the cystic duct, or from inflammatory processes within its walls or surrounding it.

Dilatation of the ducts or of the gall-bladder most frequently results from any stenosis of the ducts below.

GALL-STONES; CHOLELITHIASIS

Gall-stones are concretions resulting from inspissation of bile, or from the deposit of various substances from the bile. Most frequently they are formed in the gall-bladder; occasionally they originate in the bile-ducts.

Etiology.—The causes are imperfectly understood. Advanced years, the female sex, sedentary life, and high living seem to be factors of importance. Inflammatory conditions leading to obstruction and retardation of the outflow of bile, and also to desquamation of epithelium, which, with mucus, serves to form the nuclei of the stones,

seem to be among the causes. Besides these conditions there are probably indefinite alterations of the bile which permit of precipitation of some of its constituents, notably cholesterol. Bacteria play an important rôle in many cases. The bacteria may by their precipitation and clumping form the nucleus of a stone, or may occasion decomposition of the bile and inflammation of the ducts. Desquamated epithelial cells and products of decomposition of the bile in the latter case form the nucleus of the gall-stone. Among other micro-organisms the typhoid and colon bacilli are of etiological importance. They are able to live for long periods in the gall-bladder.



Fig. 321.—Gall-bladder from a case of chronic cholecystitis with cholelithiasis. The interior of the gall-bladder is shown with its ribbed projections and intervening pouches, in which small and large gall-stones had been lodged.

Structure and Pathological Anatomy.—Gall-stones may be single or multiple, and may vary in size from minute granular particles of biliary sand to calculi several centimeters in diameter. When single they occur as rounded or oval masses; when multiple they are prone to be marked with facets; when formed within the bile-ducts they are elongated. Biliary sand is, for the most part, composed of biliary pigments, bilirubin in combination with calcium salts. The larger stones on section usually show a central nucleus composed of epithelium or mucus mingled with inspissated bile, surrounded by a zone of somewhat radiating and crystalline structure, composed of cholesterol. Around this may be a coat of bile-pigment. In other cases the entire stone is

formed of biliary pigments in combination with calcium salts or, more rarely, the calculus consists entirely of carbonate of lime.

It seems that when stones form in a bladder that has been isolated from the liver by fibrous tissue or compression, they are usually cholesterol derived from the bladder wall. On the other hand, when there is continued inflammation, but with no hindrance to the ingress of bile from the liver, stones are mostly of bile-pigments, precipitated by bacteria probably, and calcium salts from the inflammatory exudate.

Gall-stones may lie in the gall-bladder or ducts without causing serious disturbances, or from time to time attacks of biliary colic denote their passage through the ducts to the bowel. They may pass through the ducts into the intestine when of small size, but often become impacted in the lower part of the common duct, generally just above the duodenal papillæ or in the mouth of the cystic duct. Secondary changes in the gall-bladder (dilatation and inflammation) and in the liver (enlargement, cirrhosis) may result; and the stone may cause local ulceration, and may finally escape into the bowel or into other parts by ulceration. Occasionally gall-stones remain impacted for long periods without causing serious disturbances, enough space remaining to permit the escape of bile.

TUMORS

Tumors of the biliary tract are more common than formerly thought, and are almost always malignant epithelial growths. *Primary carcinoma* arising from the mucous glands, either at the fundus or neck, which places are those at which a stone would exercise most pressure, is the most important. It is usually columnar-celled carcinoma of the adenoma type. It appears as an irregular elevation of the mucous surface, and rapidly infiltrates the adjoining parts. In cases of primary cancer of the gall-bladder the liver is soon involved. Gall-stones are present in a great majority of the cases and probably play an important etiological part by their continuous irritation. On the other hand, the gall-stones may form in consequence of the stagnation of bile and other local conditions caused by the tumor. *Secondary carcinoma* of the gall-bladder or ducts most frequently results from cancer of the liver. The lower end of the duct may be involved in cases of carcinoma of the papilla of Vater. *Sarcoma*, *fibroma*, and other tumors are rare.

JAUNDICE

Jaundice, or icterus, is a discoloration of the skin and other parts, resulting from the presence in the blood of biliary pigments.

Etiology.—Jaundice has been described as being of two forms: the *obstructive mechanical* or *hepatogenous*, and the *non-obstructive* or *hematogenous* variety. This distinction has been questioned on the assumption that bilirubin can only be formed in the liver. Late observations would seem to indicate that under certain circumstances such a process may occur in the blood, thus strengthening the above classification.

Among the distinctly mechanical causes of jaundice the most fre-

quent is occlusion of the ducts by catarrhal duodenitis and cholangitis. To this form the term *catarrhal jaundice* is generally applied. Less commonly obstruction may be occasioned by foreign bodies, gall-stones, or parasites within the ducts; by the pressure of tumors of the duodenum, pancreas, and the lymphatic glands of the liver or of the gall-ducts themselves; by the pressure of aneurysms upon the ducts; or by occlusion of the biliary passages within the liver by abscess, hydatid cysts, hypertrophic cirrhosis, carcinoma or other tumors. Congestion of the liver may lead to jaundice by the swelling of the organ consequent upon the overfilling of the vessels with blood, or by reason of the resorption of bile due to the alterations of pressure of the blood in the different vascular channels. Hematogenous jaundice was formerly regarded as due to disintegration of the blood in the general circulation, but it is now recognized that formation of the pigments normally takes place in the liver, the cells of that organ breaking up hemoglobin, keeping the iron, and using the rest of the pigment as bilirubin. From late experiments of Whipple and Hooper it seems that under certain circumstances bilirubin may be formed without the function of the liver, and a true *hematogenous* jaundice arise. There are instances of jaundice in which active hemolysis in the circulation is an element of importance, probably when the liver cannot care for all the liberated pigment as indicated above. Jaundice of this character occurs in various severe infections, such as yellow fever, acute yellow atrophy of the liver, the jaundice of the newborn, and in consequence of certain intoxications (phosphorus, toadstools, the venom of snakes). Several explanations may be applied to cases of this kind. Sometimes excessive blood destruction leads to formation of abnormally large quantities of bile (*polycholia*), and, in consequence, to absorption of biliary pigment by the lymphatics in the liver. It is believed by some investigators that the hepatic cells may in some conditions reverse the direction of their secretion, so that the bile is discharged into the lymphatic current instead of into the biliary capillaries. This view needs confirmation. In other cases toxic degeneration of the hepatic cells may lead to stimulation of the hepatic function, or to swelling of the cells and compression of the biliary capillaries, and, in consequence, to absorption of the bile. Finally, in the jaundice of the newborn, as well as in some instances of sudden emotional jaundice, disturbance of the circulation within the liver may be a potent cause.

Pathological Anatomy.—Microscopical examination of the liver may show the biliary capillaries distended with bile and the hepatic cells themselves more or less pigmented. The bile is absorbed by the lymphatics, and ultimately reaches the general circulation and pigments the tissues. The earliest evidence is seen in the intima of the vessels; later, all the tissues and organs of the body may be involved, and visible discoloration appears in the skin and external mucous membranes. The urine is dark brownish or greenish in color, and all of the secretions and liquid exudates may be pigmented. In cases caused by obstruction of the bile-ducts the bile cannot reach the intestines and the stools have a quite characteristic putty color. In "hematogenous" jaundice the

color of the stools is to a certain extent maintained. Intense disturbances, especially of the nervous system, result from excessive cholemia, but are due to the cholic acid salts rather than to the biliary pigments.

THE PANCREAS

CONGENITAL ABNORMALITIES

Complete absence has been met with in monstrosities. More frequently an adventitious pancreas or heterotopic pancreatic tissue is observed. Small nodules of pancreatic tissue may be found in the omentum, the wall of the intestines, or elsewhere. In a small percentage of cases the duct of Santorini is present as a tube of appreciable size discharging into the duodenum.

CIRCULATORY DISTURBANCES

Active hyperemia occurs during digestion and in association with acute inflammation.

Passive hyperemia occurs in cases of obstruction to the portal circulation, but rarely leads to notable changes. The grayish-blue color is characteristic.

Hemorrhage may occur in the pancreas, in the form of minute petechiæ or diffuse hemorrhagic infiltration, as the result of passive congestion or of various hemorrhagic and infectious diseases, such as purpura, scurvy, septicemia, or the extreme anemias.

Large hemorrhages occur in what is called "acute hemorrhagic pancreatitis." By some the inflammatory nature of this condition is denied, but because of the cellular and serous infiltration accompanying it we prefer to describe it under pancreatitis and to call the hemorrhage without any infiltration "pancreatic apoplexy." Moreover, it is probable that some infection, recent or remote, has induced it (see below). Traumatic hemorrhage does occur.

Pancreatic apoplexy is a suddenly appearing destructive hemorrhagic extravasation into the organ without preceding inflammatory change, said to be due most often to alcohol, at times following injury, and occasionally occurring without discoverable cause.

Sudden death may occur in these conditions from shock or compression of the solar plexus, or the case may terminate in other pancreatic affections. Doubtless chronic indurative pancreatitis originates in this way in some cases. More commonly, progressive necrosis and suppurative inflammation terminate the disease.

ATROPHY AND DEGENERATIONS

Atrophy of the pancreas occurs in old age and as the result of marasmic conditions. The entire organ is involved in such cases. Localized atrophy may be associated with various degenerations or other diseases of the organ. Thus, in carcinoma or in cirrhosis, pressure-atrophies are extremely frequent.

Parenchymatous degeneration may occur in consequence of acute infections, and resembles the cloudy swelling of the liver, kidneys, and

heart occurring in the same diseases. The organ becomes somewhat enlarged, is softer than normal, and may at the same time be congested. Microscopically, the cells are found to have undergone granular change (parenchymatous degeneration).

Amyloid infiltration is a rare condition occurring in association with amyloid disease of other organs.

Pigmentation may be met with in the atrophic organ of old persons, or in consequence of hemorrhagic infiltration and subsequent disorganization of the extravasated blood. Of particular interest are the cases of *hematochromatosis* affecting the pancreas, together with the intestines, liver, and other abdominal organs in drunkards. The affected organs in this condition present more or less extensive hematogenous pigmentation.

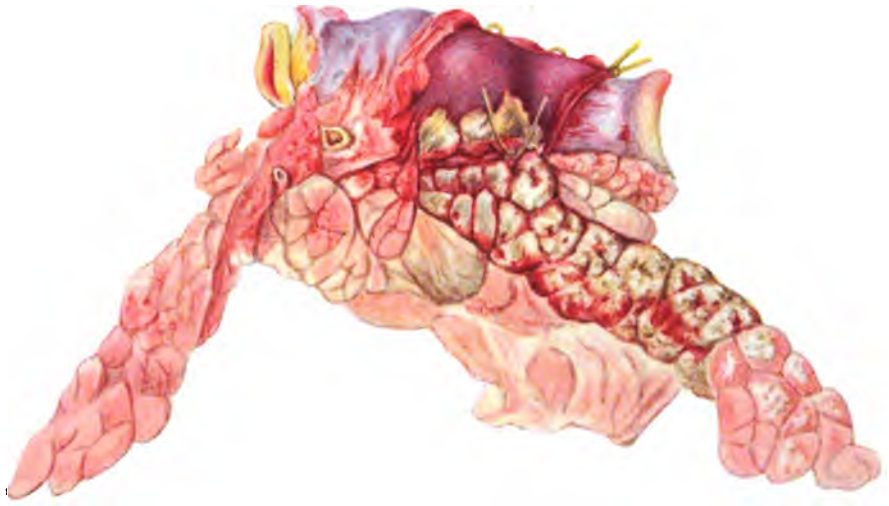
Necrosis of small areas of the pancreas may occur in consequence of hemorrhagic or of inflammatory conditions. Sometimes the entire organ is disorganized by a form of gangrenous necrosis, especially in cases of pancreatitis resulting from perforation of a gastric ulcer or from extension of other severe inflammatory lesions. This is a form of self-digestion due to active enzymes, liberated either by disturbance of the blood-supply or infection. Autolysis may occur at times as a post-mortem change.

Disease of the Islands of Langerhans.—The pancreas normally contains small collections of round cells differing very strikingly from the true pancreatic cells. They are more abundant near the tail than the head of the organ. They are not in relation with the excretory ducts of the organ, but rather with the blood-vessels, and are supposed to make an internal secretion. Atrophy and hyaline degeneration of these islands have been described in association with chronic interstitial pancreatitis and as independent conditions. The relation of such lesions to diabetes is discussed below.

Fat necrosis is a form of degeneration or necrosis peculiar to the fatty tissue of the pancreas and of the omentum. Most frequently it is found in association with acute or chronic pancreatitis, with tumors of the pancreas, or obstruction of its duct; but it may occur independently, and it may appear in the fatty tissue of the omentum without involving the pancreas. Minute foci, having a gray or white, opaque appearance, or, more rarely, larger areas due to confluence of small foci of necrosis, are found in the adipose tissues. Hemorrhagic infiltration may be associated, and sometimes extensive hemorrhage may ensue. Inflammation of the pancreatic tissues around the foci of necrosis is common, and in some instances extensive disorganization (necrosis) of the pancreas occurs.

Microscopically, the changes consist of, first, disintegration of the fat-drops of the adipose cells with formation of small droplets, then the appearance of fat-crystals within the adipose cells, and subsequently the disorganization of these and the formation of calcium salts of the fat-acids, the microscopical appearance at this stage being that of indefinite granular or translucent masses. The nature of fat-necrosis has been previously discussed (see p. 111).

PLATE 12



Acute hemorrhagic pancreatitis showing fat necrosis.

INFLAMMATIONS

Pancreatitis may be acute or chronic. The acute variety presents itself in different forms, the most frequent being the hemorrhagic and the suppurative or necrotic. Chronic pancreatitis is analogous to chronic hepatitis, and leads to similar induration or cirrhosis.

The sources of infection of the pancreas must be the blood, lymph, and pancreatic duct, of which the last seems the most important. In disturbances of the duodenum bacteria may pass from the ampulla of Vater along Wirsung's duct to the gland, and it has been shown that bile may also follow this course. Either of these factors can produce inflammation of the duct, its sheath or adjacent acini, and lead to alterations in blood-supply to the whole organ or isolated lobules. These facts are important to remember in studying the diseases of the pancreas. In all forms of pancreatitis the existence of biliary calculi should be sought, as stones and sand, especially in Vater's ampulla, seem to predispose to affections of the organ.

Acute hemorrhagic pancreatitis occurs most commonly in young persons, and is probably in most, if not all, cases dependent upon infection of the pancreas through its ducts, in the presence of conditions favoring pancreatic hemorrhage (*q. v.*). It is likely that some cases are not actively inflammatory, but simply instances of degenerations of the pancreas, with hemorrhage and round-cell infiltration as consequences. The pancreas is swollen, especially at its head; the lobules are enlarged and the interlobular tissues compressed. Hemorrhagic infiltration is a constant condition, but variable in extent. Microscopically, the cells of the pancreas are swollen, and usually present the appearances of parenchymatous degeneration. The interlobular tissues are infiltrated with round cells. Localized necrosis and fat-necrosis may be associated. Gangrenous pancreatitis is frequently described, but this form is probably not a special variety, being more likely a severe grade of the hemorrhagic disease; it is not peculiar in causation. Rapid death is the usual consequence, but it is probable that some of the cases terminate in chronic pancreatitis. There is edema or hemorrhage into the capsule, which may escape to the peritoneum by osmosis or rupture, carrying pancreatic enzymes with it.

It is believed that the pancreatic secretion itself plays the chief rôle in the causation of this condition, since a ligation of Wirsung's duct will bring about an analogous inflammation. If local areas have been the seat of inflammation or edema, cellular necrosis will liberate the pancreatic enzymes, of which steapsin will at once attack the neighboring fat, causing fat-necrosis, while trypsin will erode blood-vessels, permitting edema or hemorrhage.

Acute suppurative pancreatitis may result from direct extension of septic processes in the neighborhood, as in gastric or duodenal ulceration, purulent collections in the peritoneum, and the like. It may also occur as an independent affection, most frequently in consequence of infection from the intestinal tract through the ducts, or as the effect of pyogenic

cocci operating in an organ devitalized by acute hemorrhagic pancreatitis. Occasionally metastatic abscesses are observed in the pancreas. Hemorrhagic pancreatitis may be converted into the necrotic form in consequence of extensive extravasation of blood and secondary infection.

The organ presents a variable appearance, according to the cause and extent of the process. There is generally marked swelling with more or less softening, and not rarely necrotic foci. Complete gangrene or necrosis is an occasional termination. In other cases parts of the pancreas may slough, the cast off part being retained as a sequestrum or discharged through the intestines or into the peritoneum, setting up fatal peritonitis. The great edematous swelling of the capsule in both the foregoing forms is worthy of emphasis.

Chronic indurative pancreatitis, or cirrhosis of the pancreas, may be hematogenous in origin, resulting from syphilis and alcoholism, or it may be caused by prolonged irritation exercised through the pancreatic ducts, calculi, either biliary or pancreatic, in consequence of frequent entrance of intestinal contents or partial stenosis of the ducts. In the latter case it may be secondary to duodenal catarrhs or obstructions of the pancreatic duct. In some cases it is doubtless the outcome of acute attacks.

The pancreas in the earlier stages is enlarged and hard, especially at the head, where the firmness may be that of scirrhus cancer. On section it may present a homogeneous structure and may be of cartilaginous consistence. Macroscopically, the tissues between the acini are visibly infiltrated and hyperplastic, the amount of connective tissue being greatly in excess of the normal. In the later stages the organ becomes contracted, and may be considerably reduced in size and of stony hardness.

Microscopically, the parenchyma of the organ is found to be atrophied or degenerated in consequence of contraction of the hyperplastic fibrous tissue. Fat-necrosis and fatty degeneration of the pancreatic cells are frequently associated.

Interlobular and interacinar fibrosis have been described. The former, said to follow infection through the duct or obstruction by calculi, produces a hard nodular organ traversed by wide trabeculae which compress the acini and islands of Langerhans. Interacinar fibrosis, believed to be due to alcohol and arteriosclerosis, occurs as a connective-tissue overgrowth within acini and islets; the organ is smooth and of natural size. This form is seen frequently with hepatic cirrhosis and diabetes.

Pathological Physiology of Pancreatic Disease.—Among the more or less characteristic symptoms of pancreatic disease are fatty diarrhea (steatorrhea), imperfect digestion of proteins (azotorrhea), rapid emaciation, lipemia, and lipuria. All of these result from the cessation of pancreatic secretion and consequent disturbances of digestion and absorption of food. None of them is pathognomonic. A more important symptom is glycosuria, and the rôle of pancreatic disease in the pathology of diabetes is a leading one. Atrophy and car-

cinoma of the organ may be found in diabetes, but the commonest changes are hyaline necroses of the islets of Langerhans and more or less regularly distributed fibrosis. Whatever the nature of the disease, the result seems to be a disturbance of an internal secretion having importance in the consumption of sugar. When this secretion stops or diminishes, glycosuria or diabetes results. While many, indeed, probably most, cases of diabetes show pancreatic lesions either in acini or islets of Langerhans, there is no anatomical proof that disease of this organ is the cause of diabetes, although chemical studies connect the two physiologically. There seems to be an internal secretion of the organ, probably emanating from the islets, which has a part in carbohydrate metabolism.

INFECTIOUS DISEASES

Syphilis may occur in the pancreas in the form of indurative pancreatitis or of gummata. The former may occur in adults, but is more common in the newborn, in association with indurative changes in the liver, lungs, and other organs.

Tuberculosis of the pancreas, in the form of miliary tubercles, may occur in cases of generalized tuberculosis, but this organ is one of the rarest seats of tuberculosis in the body.

TUMORS

Carcinoma.—Primary cancer may affect the head or, more rarely, other parts of the pancreas, and is of the glandular (scirrhus) or, more rarely, of the cylindrical-celled variety. Compression with secondary cystic distention of the pancreatic duct and obstruction of the common bile-duct or of the veins (portal, superior mesenteric, and splenic) behind the head of the organ may result. Metastasis to the neighboring lymphatic glands and to the liver is frequent. Secondary cancer may affect the pancreas by extension of cancer of the stomach or of the duodenum.

Pathological Physiology.—Pancreatic carcinoma and other chronic diseases of the pancreas often occasion rapid emaciation, and sometimes fatty diarrhea, lipemia, and lipuria. In a mechanical way cancer of the head of the pancreas may cause jaundice by obstruction of the bile-ducts; splenic enlargement, intestinal congestion, diarrhea, and ascites by obstruction of the adjacent veins; repeated vomiting and sometimes intestinal obstruction by compression of the duodenum.

Sarcoma is rarely primary. Secondary nodules are occasionally observed.

Cysts of the pancreas may be of several kinds. Dilatation from obstruction of the pancreatic duct or its branches may occasion a single cyst or multiple cysts filled with serous or gelatinous liquid. Hemorrhagic cysts are sometimes the result of necrosis of portions of the organ, or a hemorrhage (hematoma) may be later converted into a serous cyst. The latter is the mode of formation of some of the large cysts, occurring, for the most part, near the tail of the pancreas. In other

cases, it has been held, these cysts result from primary necrosis and subsequent digestion of the necrotic area by the pancreatic secretions. In rare instances cysts of the pancreas have a glandular structure of the papillary cystadenoma type.

Cystic accumulations in the lesser omental cavity, resulting from localized peritonitis, may be difficult to distinguish from true pancreatic cysts, as some of the latter lie more outside than within the pancreas. In some instances such localized peritonitis seems to be the result of extension of pancreatic inflammations or rupture of sub-capsular collections. These have been called pseudopancreatic cysts.

The fluid of pancreatic cysts often contains a proteolytic and an emulsifying ferment, but the contents of other abdominal cysts may have similar constituents.

The Pancreatic Duct

Obstruction of the pancreatic duct may be due to tumors of the papilla in the duodenum or of the head of the pancreas, to calculi, to



Fig. 322.—Dilatation of the pancreatic duct and atrophy of the pancreas, due to calculi (Orth).

inflammatory thickening of the duct itself, or to the pressure of contracting fibrous tissue in chronic pancreatitis. Most commonly it leads to *dilatation of the duct*, this sometimes becoming so great as to occasion actual cystic formations (Fig. 322). The dilated ducts are filled with clear liquid, but sometimes through bacterial infection this is rendered turbid, or is actually converted into pus. Occasionally, small cysts, caused by distention of the finer divisions of the duct, are scattered through the organ (*pancreatic acne*). These are supposed to result from catarrhal processes in the ducts themselves. These small cysts are filled with clear or puriform liquid. Some cases so described are doubtless instances of fat-necrosis. In congenital atresia of the bile-ducts there is frequently a similar condition in the duct of Wirsung. The duct of Santorini has been found stenotic also.

Pancreatic calculi are composed of carbonate or phosphate of lime, and usually have an irregular shape. They may occasion cystic distention of the ducts and abscess formation.

THE PERITONEUM

CONGENITAL ABNORMALITIES

Absence of the peritoneum has been described; but more frequently minor defects, such as absence of the omentum or unnatural length of the omentum or mesentery, localized defects, fenestrations, and the like, have been observed. The peritoneal extension into the inguinal canal normally becomes occluded, but may remain patulous and may lead to congenital hernia.

The defects of the peritoneum are not of great importance to this structure itself, but as it acts as a protective covering and support to the abdominal viscera, alterations in position, form, and function of the contents of the cavity result from congenital defects, *e. g.*, enteroptosis from long mesentery.

CIRCULATORY DISTURBANCES

Active hyperemia may occur in association with inflammation, or in the vicinity of lesions within the intestine which have not yet occasioned actual inflammation of the peritoneum itself. The affected part is bright red, the arterioles being distended and the endothelium somewhat swollen and elevated.

Passive hyperemia is more frequent. It may be part of a general venous congestion, or may result from obstruction of the portal vein by thrombosis, cirrhosis of the liver, and similar conditions. The venules may be widely dilated, the deeper layers of the peritoneum somewhat edematous, and the lining endothelium swollen and loosened. Intense passive congestion may lead to ascites or to hemorrhage.

Hemorrhage may occur in the form of punctate extravasations in various septic and hemorrhagic diseases, and in parts adjacent to intense lesions, as in the peritoneum covering the bowel near anthrax ulcerations. Hemorrhagic extravasations may likewise be due to intense passive congestion, as in death from suffocation or in obstructions of the portal circulation. Certain forms of intoxication, like phosphorus-poisoning, snake-venom, or the like, may occasion petechial ecchymosis or large suffusions; and occasionally hemorrhagic extravasations are due to embolic occlusion of the mesenteric arteries. Large hemorrhagic effusions may occur in the retroperitoneal tissues, especially at the root of the mesentery, between the folds of the omentum, or elsewhere into the subperitoneal cellular tissues. These, as well as hemorrhages into the peritoneal cavity itself, are frequently traumatic in origin. Rupture of the spleen, of the liver, of the uterus or Fallopian tubes, or of aneurysms or superficial blood-vessels may be the immediate source of large hemorrhages.

The extravasated blood within the cellular tissues undergoes gradual absorption, as elsewhere, and may leave pigmented areas and fibrous thickening. The blood within the cavity of the peritoneum may be

directly absorbed, or may be gradually removed after clotting by degenerative processes and absorption through the lymphatic channels. Inflammatory reaction is wanting unless the blood mass is infected. Besides transudates, now to be described, air or bile may be found within the peritoneum, almost always resulting from rupture of some viscus. Gas, on rare occasions, is produced by some micro-organism.

Dropsy of the peritoneum, or ascites, may occur as a part of a general anasarca in cardiac or renal disease, or may be due to obstruction of the portal circulation, notably by cirrhosis of the liver. In these cases ascites may be absent at first from the freedom of the collateral circulation established between the branches of the inferior and superior vena cava and the peripheral radicles of the portal circulation. Eventually, however, ascites ensues. In the earliest stages of certain cases of intense acute peritonitis and in chronic peritonitis, especially the tuberculous form, when the absorption of liquid from the peritoneum is disturbed by occlusion of the lymphatics, the liquid effusion may have a serous and not the ordinary inflammatory character. Chronic peritonitis plays a part in the etiology of many cases of ascites ordinarily regarded as the result of obstruction of the circulation alone, as in cases of cirrhosis of the liver. In such cases the venous stasis may occasion no dropsical exudation until a low-grade chronic peritonitis has developed, when the membrane becomes more permeable and effusion results.

An occasional cause of ascites is obstruction of the thoracic duct by new growths of its walls, thrombosis within, or pressure from the outside. The ascitic liquid in such cases frequently has a chylous character. Solid tumors of the ovary are commonly associated with ascites.

The abdomen in ascites is filled with clear watery or yellowish liquid. Gelatinous masses (coagulated serum) often form in the dependent parts, as in the pelvis and iliac fossæ. Occasionally the liquid is quite hemorrhagic; in other cases it is milky from admixture of chyle or lymph (*chylous ascites*): The latter cases are dependent upon obstruction or rupture of the lymphatic channels. In other cases, especially in instances of endothelioma or carcinoma of the peritoneum, the liquid has a milky character from admixture of degenerated cells and fatty matter. The term *chyliform ascites* is sometimes applied to such cases. Microscopically, the liquid of ordinary ascites shows red and white blood-corpuscles and occasionally a few endothelial cells. In the hemorrhagic cases the number of blood-corpuscles is notably increased, while in chylous ascites there are fat-droplets and granular cells.

Occasionally collections of dropsical liquid occur between the layers of the omentum (*hydrops omenti*).

Ascites causes more or less serious compression and displacement of the abdominal organs. The respirations may be greatly embarrassed by upward displacement of the diaphragm, and the circulation may be obstructed by the pressure of the liquid upon the veins. Secondary changes in the peritoneum are not unusual. Long-standing ascites

nearly always gives rise to a certain amount of chronic inflammation (fibrous thickening of the membrane), and terminal tuberculous infection of the peritoneum is not infrequent.

INFLAMMATIONS

Inflammation of the peritoneum, or peritonitis, is the most important condition of this structure. Acute and chronic cases may be distinguished. The latter, in most instances, merely represent terminal conditions following acute forms of the disease. Exceptionally, peritonitis may be a chronic affection from the beginning.

Etiology.—Acute peritonitis is probably always caused by bacteria or bacterial products. It is possible to produce it in animals by injections of chemical poisons into the peritoneum, but it is doubtful if spontaneous peritonitis ever occurs excepting as a result of infection.

The bacteria gain access to the peritoneum through the blood, by direct migration from the Fallopian tubes, by invasion through the walls of the abdominal viscera, or by perforation of the viscera or external abdominal walls. Hematogenic peritonitis is sometimes met with in cases of general septicemia and pyemia, as in osteomyelitis or malignant endocarditis, but such cases are rare. In these instances the bacteria may be discharged into the peritoneal cavity from the blood, and may thus occasion a direct or primary peritonitis; more frequently a localized lesion, such as a suppurating infarction, is first produced, and the peritonitis results secondarily from this. Undoubtedly, bacteria are often set free in the peritoneum in the course of infections, but this structure seems to have a high degree of resistance, and seems to be possessed of special means of defence. The experiments of Pfeiffer with regard to the mechanism of immunity (see p. 257) may be cited in this connection. (See also note on etiology of pleurisy, p. 587, referable to serous membrane defenses.) Idiopathic peritonitis was a term used by older authors to designate forms of seemingly causeless peritonitis, or such as follow exposure to cold and the like. At the present time we must regard these as exceptional instances of primary hematogenic peritonitis or, more commonly, as cases of secondary peritonitis resulting from abdominal infections that have been overlooked.

Peritonitis resulting from direct extension of infective processes is very common. A certain amount of irritation of the serous coat (the peritoneum) of the abdominal organs occurs in most of the diseases of these organs, and in the case of certain infectious diseases this may attain considerable intensity. For example, in cases of ulcers of the intestines or strangulation of a coil of intestine with secondary necrosis, considerable peritonitis, local and eventually general, may occur without perforation of the gut. In such cases the bacteria penetrate the walls of the intestines along the lymphatic channels, and thus reach the serous covering. Similar extensions are found in diseases of the tubes and ovaries, or of the uterus in puerperal sepsis.

Perforative peritonitis is the most important of the forms. It may

result from perforation of gastric ulcers or cancer, from traumatic or ulcerative perforations of other parts of the intestinal tract, from perforation of the appendix in acute appendicitis, or from rupture of diseased Fallopian tubes; less commonly perforation of the other abdominal viscera, or rupture of infective foci, such as abscesses of the spleen, liver, pancreas, ovaries, or other structures, or penetration of the abdomen from without by stab-wounds or disease, may lead to peritoneal infection.

Among the micro-organisms that have been detected, the *Streptococcus pyogenes* is most important, and is the cause of the severest forms of peritonitis, such as those occurring in puerperal sepsis. Occasionally the disease is due to the *Staphylococcus pyogenes*, the *Bacillus coli communis*, the *Diplococcus pneumoniae*, the *bacillus of Friedländer*, the *gonococcus*, or other organisms. The *Bacillus coli* is mainly operative in peritonitis secondary to intestinal diseases, such as appendicitis. Very often, no doubt, peritonitis is the consequence of mixed infection.

Pathological Anatomy.—Localized and general peritonitis may be distinguished.

Acute localized peritonitis is seen in cases in which bacteria escape gradually and in small numbers through the walls of the viscera, or in instances in which perforation takes place after exudate has formed a wall capable of limiting the extension of the infection. Localized peritonitis is most frequent in the pelvis in association with diseases of the tubes or uterus, and in the region of the appendix. The peritoneum in the area of disease first becomes intensely injected (congested), and the normal luster disappears in consequence of the beginning exudation and disease of the lining endothelium. Subsequently the amount of exudate increases. It may, first, be of serous character, but usually is largely fibrinous, and the amount may be considerable. Thus, the appendix is not rarely surrounded by masses of fibrinous exudate a centimeter or two in thickness. The exudate may remain fibrinous, but more frequently becomes fibrinopurulent in the later stages; and in cases of perforative peritonitis localized abscesses are commonly met with. In such cases, if the disease remains well encapsulated and the patient survives, the exudate may be removed in several ways. Very rarely the pus burrows toward the exterior and discharges; more frequently it empties into the intestine or some other hollow viscus. It may decrease by gradual inspissation, leaving a dry, cheesy mass, which in rare instances finally becomes calcareous. Fibrinous exudates in localized peritonitis are frequently absorbed, and give place to fibrous adhesions.

Acute general peritonitis may be the immediate result of the discharge of large quantities of infective matter from a perforated bowel or other organ; or it may occur secondarily to a localized peritonitis when the limiting wall of exudation is broken down. In these cases the peritoneal covering of the intestines, and to a less extent the parietal peritoneum, become congested and lusterless, as in the localized form. Serous exudation takes place, and may be considerable in amount in

some of the most violent forms of the disease. Acute inflammatory ascites is thus produced. Usually, however, the serous exudation is scanty, and very soon the intestines are covered with flakes or thin coatings of fibrinous exudate and are matted together. Subsequently the exudate grows more yellowish from the emigration of leukocytes or pus-cells. When adjacent coils of intestine are agglutinated by the exudate, pockets containing serous or seropurulent liquid may be formed between them.

In the most virulent forms of peritonitis, local or general, such as those due to strangulation and gangrene of a part of the bowel, or to puerperal sepsis, the exudates may rapidly assume a putrid character, and the deposit upon the serous surface, as well as the serosa itself, may undergo necrotic change. In these cases the cavity of the peritoneum contains more or less ill-smelling brownish, grayish, or blood-tinged liquid exudate, and the affected areas of the peritoneum are covered with greenish or brownish deposits.

Hemorrhagic peritonitis is sometimes observed. It represents no special form, but merely indicates systemic or local conditions, as a result of which hemorrhagic extravasation has taken place into the exudate. This is found in the peritonitis of scorbutic individuals or of persons reduced in vitality by other diseases. It also occurs when passive congestion is associated with peritonitis, as in cases of cirrhosis of the liver. The peritonitis accompanying tuberculosis, and especially carcinoma of the peritoneum, may present hemorrhagic exudate.

Effects of Acute Peritonitis.—The disease of the peritoneum has an immediate and profound effect upon the intestines, and reflexly or in other ways upon the general system. The peristalsis of the bowel in the earlier stages is arrested by spasmodic contraction. Very soon the musculature is paralyzed and more obstinate constipation results. The systemic effects are most strikingly evidenced by the intense shock of the early stages. General septicemia may be the consequence of the infective conditions of the peritoneum.

Chronic peritonitis may be the termination of an acute peritonitis, especially the localized form. In other cases chronic inflammatory thickening occurs in the peritoneum adjacent to or covering organs the seat of various diseases. Thus, in cirrhosis of the liver the peritoneal covering and the reflexions forming the ligaments may be greatly thickened, and similarly the peritoneum covering the spleen may be involved in consequence of chronic congestion or inflammation of this organ. These adhesions may distort organs or act as bands to constrict the intestines, under which circumstances intestinal obstruction may arise. When adhesions are numerous, peristalsis is embarrassed and constipation is common.

Chronic peritonitis following local acute peritonitis usually presents itself in the form of fibrous thickenings or adhesions, such as are so often encountered in the pelvis after uterine, tubal, or ovarian disease complicated by peritonitis, and about the appendix after inflammations of this structure. Less commonly chronic peritonitis is met with in the

form of sacculated effusions. In such instances the effusion formed during the acute stage is only partially absorbed, and remains as an inspissated liquid.

In other cases dense adhesions are formed, and occasionally calcareous plates are found in the thickened peritoneal covering of the bowels or other parts. The omentum aids in localizing peritonitis, especially of the acute exudative forms, and is actively included in the chronic stages. It is also a source from which blood and cellular elements come into the cavity of the peritoneum, since it is more vascular than the rest of the membrane.

Chronic diffuse peritonitis may result from diffuse acute peritonitis. In such cases there are widespread adhesions, and the peritoneum is more or less diffusely thickened. Considerable liquid effusion may be present. In other instances diffuse peritonitis arises in an insidious manner as a chronic process from the beginning. Some of these cases are entirely obscure in etiology; in a few it has seemed probable that syphilis was an etiological factor. The peritoneum is often uniformly thickened, but in some cases presents small nodular lesions, suggesting miliary tubercles. In several instances these nodules, together with the abundant serous effusion occasionally met with, have led to the diagnosis of tuberculous peritonitis. Microscopical examination of the nodules, however, shows a fibrous structure, and neither giant cells nor tubercle bacilli. Tuberculous and malignant peritonitis will be considered below.

Hyperplastic Perihepatitis.—A few cases have been observed of a remarkable disease in which the upper part of the parietal peritoneum and the reflexions covering the liver and spleen are greatly thickened and of dense sclerotic character—hyaloserositis. The peritoneum is sometimes several millimeters in thickness, gray or white, and suggests the appearance of the “icing” of confectioners. This has led to the term proposed by Curschmann—*Zuckergussleber*. The liver and spleen undergo more or less pressure-atrophy, and ascites is a frequent symptom. The etiology is obscure.

INFECTIOUS DISEASES

Tuberculosis may in rare instances affect the peritoneum primarily, as in cases in which tubercle bacilli penetrate the mucosa of the intestines and enter the lymphatics without causing an intestinal lesion; or in cases of infection through the Fallopian tubes. Usually tuberculosis of the peritoneum is secondary to tuberculosis of some abdominal viscus or of more distant organs. Thus, among the more frequent causes are tuberculosis of the mesenteric or retroperitoneal glands and tuberculous disease of the tubes and ovaries in women. Intestinal tuberculosis rarely leads to more than localized lesions of the serous coat opposite the ulcerations of the mucosa. Pulmonary tuberculosis may occasion hematogenic infection of the peritoneum. Simultaneous tuberculosis of various serous membranes, especially the pleura and peritoneum, is occasionally

observed. The source of infection is often hidden; sometimes the pleura is first involved and the peritoneum becomes affected by extension; less commonly the reverse occurs.

Pathological Anatomy.—Miliary tuberculosis without marked inflammatory changes may occur as a generalized peritoneal affection in acute or subacute general miliary tuberculosis. Local eruptions of similar character are seen in the pelvic peritoneum in cases of tubal or ovarian tuberculosis and upon the serosa of the intestines adjacent to tuberculous ulcers of the bowel (Fig. 323).



Fig. 323.—Disseminated miliary tuberculosis of peritoneum with caseous glands in the mesenteric stalk.

More important, from a clinical point of view, are the cases in which inflammatory changes are associated with the specific tubercle. In some instances unaccompanied by a fluid exudate extensive adhesions by fibrinous or fibrous productions are met with, while the tubercles tend to agglutinate, forming masses of considerable size and of cheesy character. The mesenteric lymph-glands may be coincidentally involved, being enlarged and caseous. Sacculated collections of serous or seropurulent liquid are sometimes observed. In another variety there is abundant serous exudation. Occasionally the exudate is hemorrhagic.

Tuberculosis of the peritoneum sometimes terminates in complete resolution, the peritoneum being left somewhat thickened, but showing no other evidences of the previous disease.

TUMORS

Fibromata and **lipomata** are sometimes met with as small nodular or pedunculated outgrowths from the subperitoneal tissues.

Sarcoma may occur in the form of diffuse gelatinous tumors of angiosarcomatous structure, or in the form of *endotheliomata*. The latter variety occasions diffuse thickening, sometimes of considerable areas, of the peritoneum. *Secondary sarcoma* is sometimes observed as nodules of considerable size or as numerous miliary nodules.

Carcinoma of the peritoneum is secondary. *Gelatinous* or *colloid cancers* of the stomach and bowel (rectum) frequently extend widely through the peritoneum, causing great thickening and a remarkably gelatinous growth. Not rarely rounded masses of pearly appearance are observed (see Fig. 91). In rare instances tumors of the peritoneum of the same general character seem to be primary, and the reasonable explanation has been suggested that parts of intestinal tissue, pinched off in fetal development, are the starting-points of the growths. *Secondary cancer* frequently appears in the form of nodular tumors in association with ovarian cystomata that have become carcinomatous, or with primary cancers of the ovaries and other pelvic organs. Thus arises the *pseudomyxoma peritonei*, a name applied because of the tendency to myxomatous degeneration shown by tumors of the peritoneum arising by continuity. The cystadenomata of the ovary seems to be able to grow on peritoneal surfaces after the primary tumor has ruptured. Occasionally widespread eruption of miliary nodules is met with as a part of *acute carcinomatosis*.

In all forms of carcinoma of the peritoneum inflammatory changes with intestinal agglutination and adhesion are frequent. Hemorrhagic exudation is not unusual. In rare cases the bowels are so firmly fused by the spreading tumor and the inflammatory exudates that they form a solid mass, which on section shows the cavities of adjacent coils of intestines separated by more or less uniform tumor tissue.

Lymphcysts are occasionally found beneath the peritoneal surface and in the mesenteries.

PARASITES

Echinococcus cysts occasionally occupy the peritoneal cavity, and may fill it almost completely. *Filaria* have been found in a few instances; and the *Linguatula rhinaria* and *Cysticercus cellulosæ* have been reported. An ameboid organism (*Leydenia gemmipara*) has been discovered in the liquid exudate of certain cases of ascites.

CHAPTER VI

DISEASES OF THE DUCTLESS GLANDS

THE THYROID GLAND

Anatomical Considerations.—The thyroid gland is a compound tubular gland, which in fetal life communicates with the pharynx at the base of the tongue by a duct. Later the duct is obliterated, and the gland becomes ductless. Microscopically, there are found acini lined with polyhedral or cylindrical epithelium, usually in a single layer. The lumen of the acinus contains more or less gelatinous or, as it is usually called, colloid material, which seems to be a secretion of the epithelium. It is composed of nucleoprotein and globulin, the latter, the *thyreoglobulin*, containing a notable proportion of iodine. The vascular supply of the gland is very abundant, the blood-vessels being numerous and the anastomoses very free. The lymphatic network is equally abundant, and mainly situated in the stroma of the gland around the acini. The larger lymphatics are supplied with valves like those of the veins. Occasionally colloid material has been found in the stroma and in the lymphatics. The capsule of the gland is a fibrous covering from which trabeculae extend into the substance of the organ.

CONGENITAL DEFECTS

Occasionally one or another part of the gland is wanting, or, in rare instances, the entire organ.

Accessory thyroid glands have been found in various situations. Sometimes small masses of thyroid tissue occur alongside of a normal gland, either above it, in the neck; or below it, behind the sternum and in the anterior mediastinum. In other cases the normal thyroid is absent, but is represented by small masses in the situations named or in other parts. In a few instances tumors at the base of the tongue and within the larynx and trachea have been found to be composed of thyroid tissue, or the thyroglossal duct remains partly patulous and cyst-like swellings arise.

DISTURBANCES OF CIRCULATION

Hyperemia of the thyroid gland is met with very frequently. It occurs in cases of cardiac failure, and in consequence of obstruction of the large veins by mediastinal tumors and the like. In these instances the thyroid may be considerably enlarged, and has a soft, doughy character. Slight enlargement of the thyroid of congestive character is found in perhaps a majority of the cases of chlorosis, and

may be present in any form of anemia and during pregnancy and menstruation. In Graves' disease the thyroid may be very vascular, and the enlargement of the gland may be in large part due to dilatation of the blood-vessels (see below).

INFLAMMATIONS

Acute thyroiditis may occur in the course of various infectious diseases, notably typhoid fever. Occasionally it arises without definite preceding disease. The gland enlarges and becomes rather tense. The termination is usually in resolution, and this may occur very rapidly, suggesting that the enlargement of the gland is due largely to congestion and liquid exudation, rather than to cellular (inflammatory) infiltration.

Acute suppurative thyroiditis, or abscess, occurs in consequence of embolism, in cases of infected wounds, endocarditis, or general pyemia. Sometimes the inflammation extends directly from local diseases, such as diphtheria. The abscess may rupture, or may undergo secondary changes—inspissation, calcification.

STRUMA OR GOITER

Definition.—Goiter is the name applied to various enlargements of the thyroid gland. It is a clinical rather than a pathological term. Sometimes a distinction is made between benign and malignant struma, the latter term including definite tumors of the thyroid gland. At the present time the term "goiter" is restricted to enlargements of a hyperplastic character, which, though often resembling tumors, cannot be definitely classified among the tumors of the gland.

Etiology.—Goiter occurs endemically in certain situations, as in Switzerland and other parts of Europe, and in various parts of this country. Sporadically, it is met with in all parts of the world. Local conditions of some kind are doubtless among the fundamental causes, but the nature of these conditions is but little known. The drinking-water has always been suspected, and it seems likely that it has some influence, though it is certain that the magnesium and calcium salts have not the importance formerly ascribed to them. Infectious causes have been suspected and micro-organisms have actually been described, but no satisfactory demonstrations have been made.

Pathological Anatomy.—Two principal varieties may be distinguished: the parenchymatous and the vascular.

Parenchymatous goiter is a variety in which the glandular tissues or acini undergo more or less active hyperplasia. The gland is generally uniformly enlarged, but sometimes presents lobular or nodular elevations. The tissue is ordinarily somewhat elastic, like that of the normal thyroid, but may in other instances be very firm. Occasionally cystic forms occur, and a subvariety is sometimes distinguished by the term *cystic goiter*.

Microscopically, there may be found merely a uniform hyperplasia of the glandular acini, without any notable change in the structure of the tissue. The hyperplasia may be so great as to simulate papillary cystadenoma (see Fig. 326). In most instances the acini contain but small quantities of colloid material, as is the case in the normal gland. Sometimes, however, there is abundant production of colloid, and the acini are greatly distended; the term *colloid goiter* may be applied in such instances (Fig. 324). In certain cases the walls of the acini are destroyed and the colloid of adjacent acini runs together, forming considerable cysts. In these instances the thyroid consists of numerous cystic excavations.



Fig. 324.—Colloid goiter, showing colloid material in the dilated acini.

Changes in the interstitial connective tissue of the gland may be comparatively slight, but may in other cases become conspicuous. The capsule of the gland may be thickened, and the stroma may predominate over the glandular elements. The term *fibrous goiter* has been suggested for such cases.

Vascular Goiter.—This term is applied to enlargements of the thyroid gland characterized by marked dilatation of blood-vessels within the organ. The glandular tissues themselves present changes similar to those described under Parenchymatous Goiter. The gland undergoes considerable and sometimes enormous enlargement, and may pulsate

actively. This form of goiter is met with as the important pathological condition of many cases of Graves' disease (see p. 707).

The alveoli vary greatly in size and form, often sending out diverticula which become constricted off to form new alveoli (Fig. 325). The epithelium is at first hyperplastic, then becomes flatter as the colloid increases in amount and density. The vascular supply is unusually rich, the veins especially being large and distended with blood, their walls being very friable. They lie, for the most part, in the increased connective-tissue framework, in which tissue are also numerous small,

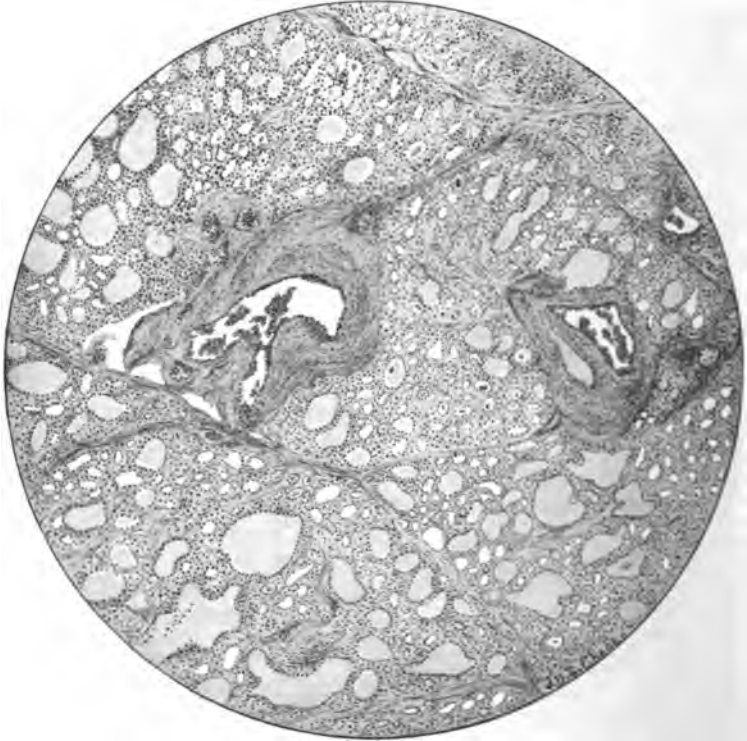


Fig. 325.—Parenchymatous and vascular goiter, showing large, thick-walled blood-vessels.

circumscribed, scattered lymphoid nodules. Corresponding with this there is an enlargement of the cervical lymph-glands and of the thymus.

The parathyroid glands show a moderate atrophy of cells and induration or increase of connective tissue, but this is by no means constant or sufficiently extensive to support the idea that these glands are in any way the cause of the disease.

There is also recognized a form of goiter in which hyperplasia, instead of being diffuse as in the two preceding types, is of a nodular character. In this case areas of active hyperplasia are mixed with normal or atrophic fields. To these cases the name *adenomatous goiter* is given. If, however, the lobular and acinus grouping should revert

to the fetal character, the name *fetal adenoma* is given (Fig. 327). It must be emphasized that these are not tumors, as their names would imply, but hyperplasias of insular character whose causation is not understood. They are actively proliferative forms, especially the latter, but may or may not give symptoms.

Relation of Histological Change to Clinical Conditions.—The function of the thyroid cells seems to be to form colloid and elaborate an internal secretion, the latter seemingly closely bound with the former. The resting gland has low cuboidal or thick flat cells, a moderate amount of colloid, little interstitial cellular content, and moderate vascularity. With hyperplasia first comes congestion, then increase in the size of the epithelium and reduction of colloid, for, with greater blood-supply,



Fig. 326.—Papillary cyst adenomatous hyperplasia of thyroid gland.

more absorption takes place. This, in any one of the anatomical forms of hyperplasia mentioned above, supplies the basis for *hyperthyroidism*. As the vascularity and, usually, interstitial cellular infiltrate increase, low-grade inflammatory changes may take place and a stage of retrogression set in. This is marked by a lower stature of the epithelium, firm colloid and fibrous tissue increase. There is less absorption at this stage, and it represents a condition possible in simple goiter. A return of hyperplasia in such an atrophic gland may again lead to toxic symptoms. It seems that the absorption of colloid is responsible for hyperthyroidism. The iodine content of fully formed colloid in normal or regressive thyroids is high, while that of the mucoid material replacing colloid in hyperplastic glands is low. What disturbs the balance and induces the hyperplasia is not known.

Secondary Changes.—The hyperplasia of connective tissue between the acini has been referred to. Sometimes this becomes so considerable that the term “fibrous goiter” is warranted. Cystic formations have also been mentioned, the cysts referred to resulting from the confluence of the dilated acini. The contents in such cases consist of colloid material or of more or less serous or hemorrhagic liquid. Occasionally cysts result from hemorrhage in degenerated parts of the gland, with subsequent absorption of the blood and exudation of serous liquid. The contents in such cases may be purely serous or may consist of brownish grumous matter containing abundant cholesterol. Very rarely secondary proliferative changes occur in the walls of the cyst, causing

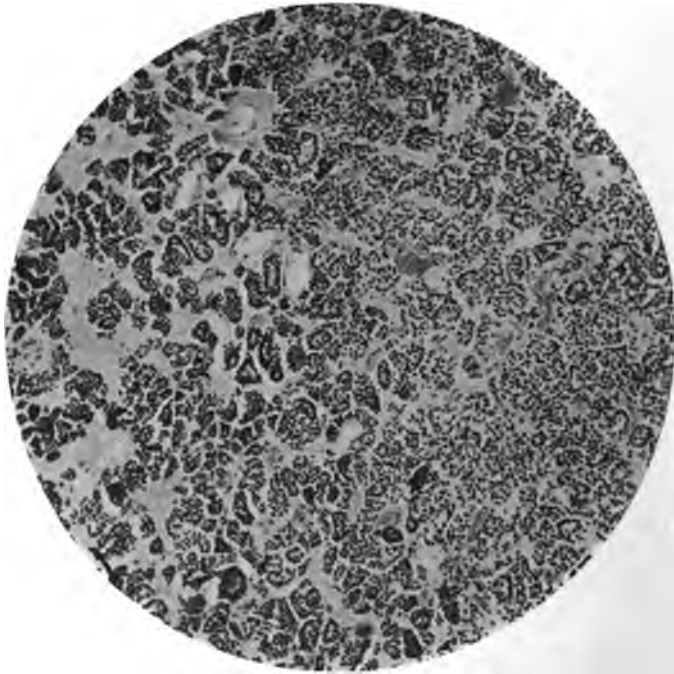


Fig. 327.—Fetal adenoma of thyroid.

papillomatous projections. Calcification is a very common terminal change in degenerated goiters. It may occur in isolated areas or may cause a uniform hardening of the gland. Actual ossification has been observed. Inflammation of a goitrous thyroid is known as *strumitis*, to distinguish it from thyroiditis.

Mechanical Effects of Goiter.—The enlarged gland presses upon the adjacent structures more or less seriously. The trachea is most frequently compressed or dislocated from its median position. Pressure upon the large veins may occasion passive congestion and edema; and less commonly pressure on the carotid artery may interfere with the circulation of blood in the brain. The nerves in the vicinity (vagus, recurrent laryngeal, and sympathetic) are likewise exposed to pressure.

INFECTIOUS DISEASES

Tuberculosis may occur in the form of miliary tubercles or as small caseous nodules.

Syphilis is met with in the form of gummata.

Actinomycosis is a very rare disease of the thyroid gland.

TUMORS AND PARASITES

Tumors.—The term “malignant struma” is sometimes applied to tumors, and it is difficult in certain cases to draw a sharp line between certain goiters and distinct new growths (adenomata).

All tumors of the thyroid have a tendency to cystic change and, as might be expected of this organ, to collections of colloid. These characteristics persist in metastases.

The term *adenoma*, however, should be restricted to cases in which the proliferation of acini is atypical, and in which the tumor is circumscribed, nodular, or otherwise distinguishable from the pre-existing gland tissue. Sometimes tumors of the thyroid having typically adenomatous characters give metastasis. The tumors are prone to assume cystic and papillomatous change.

Carcinoma may occur in the form of a nodular or more diffuse tumor. Metastasis is frequent in cases of carcinoma, but also occurs in cases that present the appearances of an ordinary adenoma. The bones are frequently involved by metastatic deposits. Extension from the thyroid to the adjacent organs is not infrequent. Carcinoma sarcomatodes has been described several times.

Sarcoma occurs in several varieties. Round-celled sarcoma and angiosarcoma are particularly malignant.

Secondary tumors in the thyroid are rare.

Parasites.—*Echinococcus* cysts have been met with, but are very rare.

GENERAL RESULTS OF THYROID DISEASE

The physiology of the gland has not as yet been fully determined, though certain facts have become established. The old authors believed the gland to be active as a blood-making organ, and this is still maintained by some. It is, however, unlikely that this function is an important one. The frequent association of thyroid disease with certain general conditions (cretinism and myxedema) has led to experiments upon animals that have established certain important facts.

In earlier experiments at removal of the thyroid gland in animals various nervous symptoms resembling those of tetany were noted. Later investigations have shown that these results were due to the simultaneous removal of the parathyroid bodies. In more recent studies care has been taken to avoid this parathyroid ablation, and it has been found that in young animals checking of ossification and stunting of growth, enlargement of the hypophysis, apathy, and other

symptoms suggestive of cretinism in man occur. In adult animals typical *cachexia strumipriva* results. This is characterized by pallor, edema of the skin, general weakness, loss of hair, and alteration of the cerebral functions (intellection, sensation, and motor power).

Removal of the thyroid causes a decrease in protein metabolism and an increased tolerance of carbohydrates without the production of glycosuria. The latter effect seems to be due to an action of the thyroid antagonistic to that of the pancreas which checks the mobilization of sugar, while the thyroid facilitates it.



Fig. 328.—Cretin.

Cretinism is a peculiar disease, occurring with great frequency in certain parts of central Europe, especially in Switzerland, and not infrequently in other parts of the world. The thyroid gland is sometimes atrophic and sometimes goiterous, but in all cases diseased. The disease is not, as a rule, present at birth, but usually develops soon thereafter; the parents may be cretinoid or goiterous, though sometimes healthy parents have cretin children. The cretin remains physically and mentally undeveloped; the subcutaneous tissue is flabby, abundant, and sometimes distinctly myxedematous (Fig. 328); the head is large; the lips and tongue thickened, and the latter often protrudes from the mouth; the hairs of the body are little developed. Lack of bony development and incomplete ossification occasion the stunted and often deformed condition of the cretin.

A distinction must be made between *sporadic* and *endemic cretinism*. In the latter the appearances are much less uniform and the mental retardation comparatively more marked than the physical evidences of cretinism.

Myxedema is a disease that develops in later life, sometimes after distinct diseases of the thyroid (goiter, gumma, tumors, etc.), but often without any manifest disease of thyroid, though atrophy and degenerations (calcification) may be disclosed by the postmortem examination. There is a peculiar swelling of the eyelids and of the subcutaneous tissue of the face and neck, and subsequently the same change occurs elsewhere, involving the limbs and the entire body. The appearances at first suggest edema, but there is not the usual pitting on pressure, and the feeling conveyed to the hand is that of an infiltration with some form of gelatinous tissue. This has been found to consist of a mucin-like substance, often associated with increase of the adipose tissue

itself. The skin of the patient is pallid and exceedingly dry; the hair falls out, and nervous symptoms are developed. Eventually, intellection may be almost destroyed.

The resemblance of these diseases to the symptoms produced by operative removal of the thyroid gland makes it certain that disease of the thyroid is the fundamental condition in cretinism and myxedema. This fact is still more clearly demonstrated by the numerous cures of these diseases following implantation of sheeps' thyroids in the peritoneal cavity, and especially the feeding of thyroid-gland tissue or extracts.

Graves' disease has been referred to in connection with goiter. The cardinal symptoms of this disease are enlargement of the gland, palpitation of the heart, exophthalmos, and muscular tremor. The pathology of the disease has not as yet been fully determined. It seems likely, however, from recent investigations that the thyroid disease, from whatever cause it may result, is the primary disorder. Removal of large parts of the gland has been found to control the symptoms of Graves' disease in a large number of cases, and the feeding of thyroid extract for a long period of time produces symptoms like those of Graves' disease: rapid action and palpitation of the heart, exophthalmos, and tremor. According to the view here expressed, the symptoms which together constitute Graves' disease are probably due to overproduction of thyroid secretion; they are, in fact, the result of *hyperthyroidism*. While the symptoms, pathological anatomy, and chemistry indicate too much thyroid, the actual state of affairs according to some writers is one of thyroid insufficiency, in that some normal secretion is diminished or perverted. It seems possible to have Graves' disease without great alterations in the anatomy of the gland, at the time seen at least. The opinion, however, is held by others that Graves' disease is primarily an affection of the nervous system.

The **parathyroid glands** are small bodies lying on or within the capsule of the thyroid, consisting of closely packed acini similar in cellular appearance to the larger gland in its fetal stage. The number varies from one to six. Their relation to the thyroids and general



Fig. 329.—The thyroid gland and parathyroid glandules; blood-supply (posterior view) (Halsted and Evans).

metabolism is not clearly understood. Their complete removal seems to cause tetany. That they have some importance in the calcium metabolism and that this latter stands in some relation to tetany is indicated by a disappearance of tetany upon the introduction of calcium salts. In some way these glands regulate the deposit of calcium salts in bone. The parathyroids are sometimes the seat of hyperplasia or true tumors.

THE SUPRARENAL BODIES

Anatomical Considerations.—The suprarenal bodies are composed of a cortical and a medullary portion, and are enclosed in a fibrous capsule from which septa extend into the substance of the organ. The cortical portion is composed of columns of polygonal cells filled with doubly refractive granules of lipoid substance. Three layers are distinguishable in the cortex: an outer zone, in which the cells are arranged in oval masses (*zona glomerulosa*); a middle zone, in which they form cylindrical columns extending toward the medulla (*zona fasciculata*); and an inner zone, composed of irregularly anastomosing columns of cells (*zona reticularis*). The cells of the middle zone are the most markedly granular. The medulla of the gland consists of similar polygonal cells arranged in cords or irregularly anastomosing columns, and contains numerous non-medullated nerve-fibers and multipolar nerve-cells, as well as aggregations of cells which are stained brown by chromic acid (chromaffin cells). These cells are derived from the neuroblasts of the central nervous system and are found distributed in various situations as a "chromaffin system." Among these situations are the sympathetic nerves, the root of carotid arteries, the left coronary, the superior mesenteric, the solar plexus, etc. In all these situations the chromaffin cells doubtless have the same functional action—manufacture of adrenalin or epinephrin—as in the suprarenal bodies.

Physiological Functions.—The important function of the suprarenal gland, thus far determined, is the manufacture of epinephrin by the chromaffin cells. This substance has the general effect of stimulating the peripheral ends of the nerves of the true sympathetic system, owing to which it causes marked rise of blood-pressure. Probably the same action accounts for the occurrence of glycosuria following injections of epinephrin, the action in this case being upon sympathetic nerve-fibers in the liver. This and other evidence indicates that the suprarenal glands are closely related to carbohydrate metabolism. It is believed that epinephrin is diminished in nervous strain, fatigue, injury with shock, and bacterial diseases. While it is supposed to be increased in conditions with high blood-pressure, there is no proof that this secretion is high in any disease.

The occurrence of pigmentation in Addison's disease suggests a relationship of the suprarenal glands to the pigment production, but the pathogenesis is not as yet clearly determined.

CONGENITAL ANOMALIES

Accessory suprarenal bodies may be found in the vicinity of the main body. Of peculiar interest are the portions of suprarenal tissue (*cortical cells*) found in the capsule or cortex of the kidney. These "rests" may subsequently proliferate and form tumors of the kidney. (See Tumors of the Kidney.)

Occasionally the suprarenal bodies are found in unusual situations.

Malformations of the adrenal system seem to be connected with similar changes in the nervous and genital organs.

DEGENERATIONS

Fatty degeneration is normal in adults. It affects the cortex, giving this layer a yellowish color. The substance of the cortex may separate through the middle zone, forming a cavity suggesting a cyst. This is probably in part a postmortem production.

Pigmentation is observed in the cells of the medullary portion, especially in persons of advanced age.

Amyloid infiltration occurs in connection with amyloid disease of other organs. The suprarenal body becomes hard and of a grayish, translucent appearance. The degeneration affects the walls of the blood-vessels, from which it extends to the connective tissue. The glandular portions suffer pressure-atrophy. The cortex is more frequently involved than the medulla.

INFECTIOUS DISEASES

Tuberculosis of the suprarenal body is the most important of its diseases. *Miliary tubercles* may be met with in cases of general tuberculosis, but a *fibrocaseous form* of the disease is more frequent and of much greater significance. The gland is enlarged, sometimes reaching the size of an egg; it is hard and usually rather nodular or irregular in outline. The capsule is thickened, and the substance of the gland is composed of dry, yellowish, cheesy matter, or of a puriform material. In the later stages the caseous or puriform matter may be inspissated, and fibrous-tissue growth may convert the entire body into a shrivelled, hard mass of connective tissue. Sometimes one gland alone is involved; more frequently the disease occurs bilaterally. Tuberculosis of this form may be primary, but usually is secondary to tuberculosis of the lungs, intestines, or other organs.

Addison's disease, in which fibrocaseous tuberculosis of the suprarenal bodies is commonly present, is an affection characterized by brownish pigmentation of the skin of exposed parts of the body (face, neck, and hands), and of the skin in the flexures of the joints or in other parts subjected to pressure. The pigmentation usually occurs in a mottled form at first, but soon becomes uniform. Brownish or purplish spots upon the mucous membranes (mouth) are not unusual. Besides

pigmentation the characteristic symptoms are great weakness, disturbances of the stomach (vomiting), and cardiovascular asthenia.

Though fibrocaceous tuberculosis of the suprarenal gland is discovered in many cases, Addison's disease may occur in association with other affections of the suprarenal, such as tumors; and it may be absent despite the existence of tuberculosis or of other diseases of both of the glands. The absence of Addison's disease in the latter cases has been explained by some writers by the assumption that the suprarenal disease had not existed long enough for the development of the symptoms of Addison's disease. Occasionally, alterations in the sympathetic nervous system (semilunar ganglia and solar plexus) have been discovered when the suprarenal glands were apparently normal. No explanation of such cases can be made. It must be accepted at the present time that the suprarenal bodies are in some way concerned in the etiology of the disease, but it is impossible to state how much disease of the cortex and medulla (chromaffin system) respectively are concerned. It seems evident that the medulla is more largely involved, and disease of the chromaffin system outside the adrenals may explain the cases of Addison's disease without lesions of these glands. The disease of the gland need not, however, be of any special sort.

Lewin found among 281 cases—typical cases of Addison's disease with sound adrenals, 20 per cent.; typical cases of Addison's disease with diseased adrenals, 80 per cent.; disease of adrenals without bronzing, 28 per cent.; disease of adrenals with bronzing, 72 per cent. In Addison's original paper he included 3 cases of secondary cancer of the adrenals.

Tumors and hyperplasia of the adrenal cortex in the young female lead to early puberty and a certain degree of masculinity, and in the male to general sexual precocity.

The carotid and coccygeal glands are a part of the system we have been discussing, but are of little importance pathologically, aside from an occasional tumor beginning in them. They are of glandular structure and contain chromaffin cells.

Syphilis occurs in the form of gummata. Uniform fatty degeneration of the suprarenal body has been met with in congenital syphilis.

CIRCULATORY DISTURBANCES

Hemorrhage is comparatively rare. It may occur in association with hemorrhagic diseases or severe anemias, especially leukemia. Sometimes it is caused by traumatism or by obstruction of the venous circulation. The hemorrhage may be inconsiderable or may be quite large. In the latter instances secondary rupture of the hematoma may cause death by intraperitoneal hemorrhage or a hemorrhagic cyst may result.

INFLAMMATION

Inflammation of the suprarenal body is very rare. A simple and a hemorrhagic form have, however, been described. Abscess may occur in consequence of pyemia, or as a secondary condition following other forms of suprarenal disease.

TUMORS

Sarcoma is the most frequent form of tumor. Melanotic as well as unpigmented varieties are met with. The tumor may reach considerable size, and may destroy the gland completely.

Adenoma may arise from the cells of the acini. Histologically, these tumors resemble the fascicular zone of the cortex, from which they doubtless arise in the great majority of cases. The tumor occurs as a nodular, irregular growth, often of a yellowish or brownish color. "Lipomatous struma of the suprarenal" is a name given by Virchow to a fatty nodular tumor growing from the cortex.

Hypernephroma may occur as a primary tumor in the suprarenal, and when found in the young is almost always associated with abnormalities of the sexual characters. In the cases of hypernephroma of the kidneys these conditions are usually lacking.

Gliomata have been described, but it is doubtful whether these tumors are true gliomata.

Neuroma is a rare form of suprarenal tumor, arising from the neural tissue in the medulla.

Secondary sarcoma and **carcinoma** are not infrequent.

Tumors of the cortex of the kidney, having the structure of suprarenal tissue, are described under Tumors of the Kidneys.

THE THYMUS GLAND

Anatomy and Development.—The thymus gland at its earliest period consists of endodermic epithelium arranged somewhat like that of an epithelial gland. Later, mesoblastic lymphoid cells and connective tissue infiltrate it; and at birth and for several years thereafter it is composed largely of tissue arranged like the follicles of lymphatic glands. It is, however, in no way a lymph organ. Here and there in the center of these may be seen concentric whorls (the corpuscles of Hassall), the remains of the original epithelial cells. After the second year of life retrogressive changes take place, and by the age of adolescence the gland is converted into a mass of fatty connective tissue.

Congenital Abnormalities.—Complete absence or various minor irregularities of the thymus may occur; at times it is found enormously hypertrophied. In the latter case the root of the great vessels, the pericardium, and heart may be covered over by the enlarged thymus,

and sudden death seems at times due to this cause. The swelling of the thymus is a part of the so-called *status lymphaticus*, and is associated with a rapid swelling of all lymphoid tissues. It is noteworthy that the medulla of the thymus is hyperplastic, while the cortex is unchanged. The cause of the condition and its fatal outcome is unknown. *Thymic asthma*, so-called, is rarely if ever due to enlargement of the thymus and compression by it upon heart or trachea. (See Diseases of the Lymphatic Glands.)

Circulatory Disturbances.—Intense *congestion* and punctate *hemorrhages* may be found in cases in which death has occurred from asphyxia.

Inflammation as a primary disease is of doubtful occurrence, but abscesses may occur in cases of general pyemia, or from extension of suppurative affections of adjacent parts.

Infectious Diseases.—*Syphilis* occurs in the form of gummata, especially in the newborn. Caseation and softening of the gumma may occur, and a resemblance to abscess is thus produced. *Miliary* or *caseous tuberculosis* occasionally invades the thymus gland.

Tumors.—The thymus or its remnant is not infrequently the place of origin of *lymphosarcoma* of the anterior mediastinum (see Fig. 58). Tumors having this origin may be recognized by their shape and by the regularity of their outlines, the lymphosarcomata (lymphadenomata) of the lymphatic glands of the anterior mediastinum having a more irregular lobulated appearance. *Ordinary round-celled sarcoma* has been described, and *epithelioma* springing from the corpuscles of Hassall has been seen in a few cases. Dermoid cysts and angiomas have been seen.

THE PITUITARY BODY, OR HYPOPHYSIS CEREBRI

The hypophysis is a small glandular organ, situated at the base of the brain, lying upon the upper surface of the body of the sphenoid bone, and further protected posteriorly by a wall, forming a cavity which is known as the *sella turcica*. It varies slightly in size, the average weight in the adult being from 0.59 gm. (Schönemann) to 0.48 gm. (Comte). It reaches its maximum between twenty-one and forty years of age.

The hypophysis is a double organ, developed from the central nervous system and from the alimentary canal. The nervous part originates from the middle primary cerebral vesicle as an evagination from the cavity. This forms the infundibulum and the small posterior lobe. The larger anterior lobe, or true *pituitary gland*, appears to arise from two sources, one, the primitive oral tissue in early embryonal life, and the other the anterior portion of the alimentary canal; both portions become contracted at their origins, fuse, and are ultimately separated from the alimentary canal, although this separation is not complete in some of the lower vertebrata. Histologically, the organ may be divided into three parts: the anterior portion of the anterior lobe is composed of somewhat polygonal epithelium enclosed in alveoli, whose walls are made up of fibrous connective tissue. These groups of cells are very irregular, although sometimes they are arranged about the

periphery of the cavity, leaving in the center a small lumen, which, more frequently than not, is filled with an oxyphilic homogeneous mass that is supposed to be colloid. The amount of connective tissue is usually relatively small, and it contains a considerable proportion of cells as compared with connective tissues of other parts of the body, and is exceedingly vascular. The cells are of two kinds, the chromophilic and the chromophobic. The former are further divided by Comte into the eosinophilic, in which the protoplasm stains deeply and homogeneously with eosin, and usually contains vacuoles; and the cyanophilic cells, in which the protoplasm colors dark blue with hematoxylin, and rarely contains vacuoles. The protoplasm of the chromophobic cells does not stain. Some authors consider that these distinctions are not morphologic, but only indicate that the different cells are in different stages of secretory activity. The posterior part (*pars intermedia*) of the anterior lobe usually contains, in man, a small bilobed cavity lined with cylindrical ciliated epithelium. In addition, there are also a few larger cavities lined by columnar or polygonal epithelium, and usually filled with colloid material. The posterior or nervous lobe consists of neuroglia tissue, and, according to Berkeley, a few ganglion-cells containing an excess of pigment, and some varicose fibers may be found in it. Kölliker, however, denies that there is any nervous tissue at all in the posterior lobe, and has been able to find nothing but neuroglia. It contains epithelial cells derived from the *pars intermedia* and a certain amount of colloid matter.

If we can believe the assertions of those who have systematically examined large numbers of these bodies, a normal gland is the exception; thus, Schönemann found only 27 normal specimens in 110 cases, and Comte 33 in 108.

Hypertrophy of the hypophysis occurs in cretinism, myxedema, and acromegaly. In some of these cases the enlargement is due to tumor formation; in others, particularly in those occurring as a result of removal of the thyroid gland, it appears to be compensatory, or rather, as the functions of this gland and the thyroid cannot be exactly identical, at least vicarious. This enlargement, often apart from tumor formation, may be very considerable. De Conlon records a case in which the hypophysis weighed 1.55 gm., and, aside from an apparent proliferation of the epithelium cells, was normal in structure.

Circulatory Disturbances.—The gland is excessively vascular. It is possible that in some cases this vascularity may increase and give rise to a true *hyperemia*, although it is difficult to be certain of this. Changes such as are found in the thyroid gland in exophthalmic goiter have certainly not been described. In case of *passive congestion* resulting from thrombosis of the cavernous sinuses edema may be present. *Hemorrhage* in the gland is a frequent agonal phenomenon. In these cases the blood-cells, normal in appearance, are found infiltrating the connective-tissue stroma. Hemorrhages during life may occasionally occur, and give rise to small, deeply pigmented areas of softening, which ultimately form scars.

Inflammation is usually secondary and suppurative. One of us has observed a case in which the anterior lobe was infected from the parotid gland, probably as a result of ascending infection along the retropharyngeal lymphatics. In this case the capsule enclosing the gland was inflamed, and there were small collections of round cells in the substance.

Degenerations.—The most important and frequent is *colloid degeneration*, the colloid material being found in the cavities of the epithelial nests, or even as small masses in the connective-tissue septa. This may be looked upon as almost physiologic. It seems to be increased in those conditions in which we have reason to suspect increased functional activity of the glands, but also is more pronounced in cases of partial atrophy. *Amyloid infiltration* occurring in the blood-vessels has been observed in cases of general amyloid disease. The walls of the blood-vessels frequently undergo hyaline degeneration in old age.

A sort of cheesy or liquefactive necrosis is also observed in the center of adenomatous formations, and is probably due to pressure-necrosis, as a result of the limited space in which the hypophysis is placed.

Infectious Diseases.—Of the infectious inflammations, the only ones of importance are *tuberculosis*, in the form of miliary tubercles, and *syphilis*, in the form of gummatous nodules. Occasionally a large single gumma has been observed.

Tumors are the most interesting and important pathological conditions that occur, and there is still considerable difference of opinion regarding their nature.

Cysts are very common, particularly a form of cystic degeneration with distention of the follicles by colloid substance. These are almost normal in old age, the only interesting feature being the atrophy and disappearance of the epithelial cells. *Teratoid cysts* have been described, but are much less frequent than would be expected from the complicated embryology of the gland. Of this nature is the *myoneuroma* described by White.

Of the pathologically malignant tumors, the most important is the *sarcoma*. This is usually round-cell or spindle-cell in type, and apparently springs from the capsule of the gland and replaces its substance, but rarely infiltrates the surrounding tissues or gives rise to metastasis. Cases have been reported as *lymphosarcoma* in which there were numerous collections of round cells in the alveoli of the connective tissue and some hypertrophy of the latter; apparently, however, no other lymphatic organs were involved.

Glioma and *endothelioma* have been seen.

Adenoma of the hypophysis causes increase in the size; the organ remains soft or may be slightly indurated, and is of normal color. The resistance of the bony structures that surround it may cause the gland to assume extraordinary shapes. Microscopically, there is proliferation of the epithelial cells, which form long tortuous and sometimes branched tubes, and often complete atrophy of the nervous lobe. These tumors have been described particularly in connection with the disease known as acromegaly.

Pathological Physiology.—Removal of the posterior lobe of the pituitary body (Paulesco) seems to show that it is not essential to life. Removal of the anterior lobe is rapidly fatal, but partial ablation is followed by decreased growth, persistence of infantile characters, fat-

ness, atrophy of the sexual glands, and enlargement of the thyroid. Feeding experiments and the use of extracts show that the posterior lobe elaborates a substance similar in action to epinephrin.. It raises blood-pressure and stimulates smooth muscle-fibres (intestine, uterus); is diuretic and galactagogue. It also affects carbohydrate metabolism, causing glycosuria when injected experimentally.

The relation of the pituitary to acromegaly first opened the way to a recognition of the functions of the gland. In the majority of cases of acromegaly, adenoma of the pituitary occurs, and investigators agree that the cases where manifest disease of the pituitary is not found, functional hyperactivity is present. Secondary involvement of the posterior lobe (hypophysis) may occasion glycosuria, and the thyroid and sex glands may also be secondarily involved.

Several types of hypophyseal disease are recognized, and it is at present difficult to determine the seat and nature of the disturbance of function.

Gigantism has been found associated with disease of the anterior lobe when this occurs in early life, as acromegaly develops when the disease occurs in later years. Both conditions are ascribed to increased function of the anterior lobe.

Infantilism, fatness, and lack of sexual development (Fröhlich's syndrome) are ascribed to decreased function of the anterior lobe.

Hyperglycemia and decreased carbohydrate tolerance are associated with primary or secondary involvement of the posterior lobe.

Polyuria (diabetes insipidus) occurs in connection with diseases of the pituitary and adjacent structures.

THE PINEAL GLAND, OR EPIPHYSIS CEREBRI

The pineal gland, or epiphysis cerebri, is an outgrowth from the roof of the posterior portion of the anterior vesicle of the brain. Its base is soon constricted, and it is finally completely separated from the primary cerebral vesicle and enclosed in a sheath of connective tissue which is surrounded by pia mater. Histologically, it is found to consist of septa of connective tissue, dividing it into numerous alveoli, in which are found epithelial cells, some of which are branched. It is very vascular, and contains a plexus of sympathetic nerve-fibers.

It has lately been asserted that this gland has something to do with nutrition in the young, assisting and regulating metabolism and growth. It is thought by some to regulate sexual development.

At all ages it contains small calcareous concretions (*acervulus*, *brain-sand*), which must, therefore, be looked upon as physiological. It is sometimes enlarged in acromegaly and cretinism; this may be a result of simple hyperplasia of the epithelial structures, giving rise to *adenomatous* or *strumous formations*, or due to neoplasms. As a result of its position it may in these conditions occlude the aqueduct of Sylvius or the veins of Galen and produce hydrocephalus. Pathologically, aside from the calcareous infiltration already mentioned,

hyaline degeneration of the blood-vessels may occur. There are usually signs of *inflammation*, more or less marked, in cases of meningitis, which may even lead to pus formation. Of the tumors, the most important are probably *sarcomata* springing from the connective-tissue septa. *Adenomata* may also occur. *Cystic conditions*, associated with the presence of hair, cartilage, and other tissues, have been described.

Tumors and other diseases of the epiphysis, aside from local effects, have been found to occasion premature growth and sexual development.

CHAPTER VII

DISEASES OF THE URINARY ORGANS

THE KIDNEYS

CONGENITAL ANOMALIES

ABSENCE of one of the kidneys is frequently observed. Occasionally one kidney, instead of being completely absent, is atrophic or hypoplastic, while the opposite kidney may undergo compensatory hypertrophy. Both kidneys may be wanting in certain monstrosities.

Congenital lobulation is quite common and is usually bilateral. The kidney is divided into separate lobes by furrows of variable depth. Occasionally there is almost complete separation into numerous lobules.

A few instances have been observed in which there was a third kidney, and usually in these cases two of the kidneys lying to one side of the spinal column were agglutinated.

Fusion of the two kidneys may occur, and there may result a single large organ, with a double pelvis and ureter lying to one or the other side, or a *horseshoe-kidney* may be formed. In the latter the two organs, which are generally displaced far downward, are united at their lower ends by a commissure passing across the spine just above the lumbosacral junction. The commissure may consist of normal kidney tissue or may be fibrous, more commonly the former.

Congenital cysts and other congenital diseases will be referred to below.

CHANGES OF POSITION

Congenital Malposition.—Not rarely one of the kidneys is displaced downward. It may even occupy the pelvis. In other cases it is displaced laterally or forward, and has been found immediately beneath the anterior abdominal walls.

Acquired malpositions may result from pressure upon the organ, or from elongation of the peritoneal reflections covering the kidney and absorption of the perirenal fat. The right kidney is more frequently displaced than the left, and the condition is especially common in women. Repeated pregnancies, the effects of tight lacing, and diseases or displacement of the liver are prominent causes. Movability or displacement of the kidney may be but a part of a general visceral descent (*splanchnoptosis*).

Several grades of movability or displacement may be distinguished. In the first, the perirenal fat is wanting, and the kidney is more movable beneath its peritoneal covering than is normal. This occurs in a large

proportion of women, and usually affects the right kidney. In more advanced grades the peritoneal reflection covering the kidney is elongated and considerable movability of the organ within the abdomen results. The kidney may be moved from side to side, downward as far as the pelvis in some cases, or upward to the normal position or under the ribs. In a third group of cases the kidney, lying within an elongated peritoneal pouch, is retained in an abnormal position by adhesions.

Results.—Twisting of the pedicle may lead to serious circulatory disturbances, or twisting of the ureter with retention of urine, sometimes causing hydronephrosis. Pressure of the displaced right kidney upon the duodenum may lead to dilatation of the stomach.

CIRCULATORY DISTURBANCES

Anemia of the kidney may occur as a part of general anemia. The kidney is light in color and rather hard in the earlier stages; but if the anemia persists, degenerative softening and enlargement may ensue.

Complete arrest of the blood-supply, produced experimentally, leads to rapid necrosis of the kidney, the organ becoming ashen-gray in color and of a homogeneous structure, so that the separate parts (cortex, medulla, pyramids) are indistinguishable. Near the cortex, where some circulation is maintained by the capsular vessels, fatty degeneration is observed. Somewhat similar changes are met with in circumscribed areas in diseases in which the circulation in branches of the renal artery is obstructed. (See Embolism.)

Active hyperemia of the kidney is generally a part of acute inflammation. It may result from irritant chemical poisons or from the toxic action of infectious poisons. The kidney is enlarged, dark red in color, and on section the cortical substance is found to be swollen and marked by dark red points—the Malpighian bodies. Sometimes punctate or linear hemorrhages may be observed. The urine is somewhat albuminous and hyaline casts occur. It is difficult to draw a sharp line between this condition and acute nephritis.

Passive hyperemia occurs in cardiac and pulmonary diseases which impede the circulation, or rarely as a consequence of thrombosis of the inferior vena cava or renal veins, or of other local causes obstructing the circulation in the renal veins. The kidney is enlarged and, on section, the cortex is found to be swollen, the substance of the kidney dark red in color, particularly in the pyramids in the vicinity of the large veins. The Malpighian bodies may be distinctly enlarged and dark red.

Long-standing passive congestion leads to reactive hyperplasia of the interstitial connective tissue of the organ, and thus to a form of *secondary interstitial nephritis*. In these cases the kidney becomes contracted, the surface somewhat irregular, and the capsule oftentimes adherent. The organ may be intensely hard and pigmented, and the term *cyanotic induration* is appropriate.

The microscopical findings include enlargement of the tufts, with loss of the epithelium and distention of the capsule with albuminous

transudate, and hyaline or connective-tissue thickening of Bowman's capsule. There are various degenerations of the parenchyma, in response to which some of the epithelium shows multiplied nuclei or enlargement of the cell to appear like syncytial cells. There may be edema, small hemorrhages, and almost always an excess of deposited blood-pigment. Hyaline casts are always found. The connective tissue is irregularly increased over the organ.

The urine in passive hyperemia is, as a rule, deficient in quantity, and contains variable quantities of albumin and hyaline or granular tube casts.

Hemorrhage.—*Punctate hemorrhages* may occur in cases of intense active or passive hyperemia, the extravasation of blood occurring in the interstitial tissues, in the uriniferous tubules, or within the capsule of Bowman. Similar hemorrhages may be observed in acute or chronic nephritis. In these cases the extravasation of blood may occur by diapedesis or by actual rupture of the capillaries. Small hemorrhages may occur in the perirenal tissues in certain of the hemorrhagic diseases. *Large hemorrhages* occur within the kidney substance only in cases of traumatism.

Edema of the kidney results from obstruction of its venous circulation. The kidney becomes enlarged and soft, and the spaces between the convoluted tubules (the primary lymphatic spaces) are distinctly enlarged. There is associated congestion in these cases. Simple edema of the kidney may result from obstruction of the urinary outflow.

Thrombosis of the renal veins or their branches is rare. It causes intense hyperemia, hemorrhages, and edema, and later necrosis and degenerations.

Embolism is very common in the branches of the renal arteries, especially in cases of disease of the aortic valves or atheroma of the aorta, with fibrinous deposits upon the atheromatous areas. The blood-vessels of the kidney correspond closely to the conception of terminal arteries, and infarction is, therefore, the usual result. In most cases the infarcts are light-colored areas (anemic infarcts) having a wedge shape, the base of the wedge being directed toward the capsule of the organ. A zone of reactive hyperemia or hemorrhage usually separates the infarct from the surrounding structures (Fig. 330). Less frequently there are purely hemorrhagic infarcts, the entire area being dark red in color. Minute emboli may lead merely to punctate hemorrhages within the kidney, or to ecchymotic extravasations on the surface.



Fig. 330.—Anemic infarcts of the kidney surrounded by a zone of hemorrhagic infiltration (Kaufmann).

The white or anemic infarcts undergo gradual necrosis and absorption, with cicatrization or encapsulation, the contents in the latter case remaining as a dry detritus. The hemorrhagic infarcts more commonly soften, and finally terminate in cicatrization or in the formation of small cysts. In cases of infective embolism the anemic or hemorrhagic infarct may rapidly break down and form a metastatic abscess.

INFLAMMATIONS

Inflammation of the kidneys may affect the substance (*nephritis*), the mucous membrane of the pelvis (*pyelitis*), or the capsule and peripheral portions (*perinephritis*).

NEPHRITIS

Nephritis is the term given to a number of forms of degeneration and inflammation of the substance of the kidney. The term "Bright's disease" is a clinical rather than pathological one, being applied to various kinds of kidney disease attended with albuminuria and dropsy. As a rule, however, the name Bright's disease and nephritis are used synonymously.

The classification of nephritis is quite difficult. Many complex classifications have been offered, but they are either inconsistent with clinical data or include too many subdivisions of main groups. There are three cardinal minute changes of nephritis—degeneration, exudation, and proliferation. These elements vary in intensity in different forms, but there seems no constant or absolute relationship between the variations or combinations and clinical observations. We retain the old classification of nephritis because it furnishes the best basis for comparison of clinical with pathological findings. All observers agree that clinical observations do not permit of accurate diagnosis of the pathological conditions in all cases, and attempts at elaborate subdivisions based upon the pathological histology are clinically useless. Under these circumstances the old and relatively crude classification here retained must still be regarded as the most satisfactory.

Nephritis may be acute or chronic; and parenchymatous, diffuse, or interstitial. The term *parenchymatous* is applied to cases in which degenerative changes in the epithelium of the tubules or glomeruli are the most conspicuous feature; the term *diffuse* is applied when exudative or proliferative changes affecting the connective tissues between the tubules and around the glomeruli and blood-vessels are associated in more or less equal proportions with the parenchymatous changes; and the term *interstitial nephritis* is used in cases in which exudative and especially proliferative changes are conspicuous.

Etiology.—Nephritis is due in the majority of cases to irritants which reach the kidney through the circulation. Intense acute nephritis may result from various poisons, particularly such as attack the parenchyma of organs, and are, therefore, known as parenchyma poisons. Among these, arsenic, mercury, phosphorus, cantharides, and turpen-

tine are conspicuous. A second group of cases, and perhaps the largest of all, owe their origin to infections of various kinds. Nephritis is a common complication or sequel of scarlet fever, cholera, septicemia, diphtheria, and many other infectious diseases. In these cases the micro-organisms themselves may reach the kidney through the circulation, as in typhoid fever, anthrax, or pneumonia, or the renal irritation may be caused by the toxins, as in cholera and diphtheria. Nephritis is common in streptococcus infections, but whether by circulating toxins or by the cocci themselves is not certain; the latter is probably more important. Certain chronic infections lead to nephritis by the action of the toxins or by slow nutritive disturbances. Such is the case in syphilis, tuberculosis, and malaria. Auto-intoxication occasions certain cases, as in the nephritis of gout and diabetes.

In the minor infections, whether focal or generalized, low grades of degeneration or inflammation may be found in the kidney. These may be diffuse or insular, and may lead to chronic Bright's disease if the insults be repeated. Thus, in subinfection there may be a continued assault of very low power, but great in the aggregate. In focal infection, again, from the tonsil or a joint for example, bacteria or their toxins may be carried by the blood to the kidney. Our newer conceptions of these subdued forms of infection may thus explain some of the cases of nephritis heretofore called *idiopathic* or *cryptogenic*, the latter term being in a sense correct, as we seldom know the source and the infecting germ.

In a small proportion of the cases nephritis results from irritants reaching the kidney through other channels than the circulation, as in pyelonephritis, a condition consequent upon inflammatory processes ascending from the bladder and ureters, or as in nephritis secondary to extrarenal disease (psoas abscess).

Low-grade renal inflammation may result from chronic congestion of the kidneys in consequence of cardiac and pulmonary disease. In many cases arterial disease, whether or not affecting the renal arteries in common with other arteries of the body, may initiate renal changes eventuating in a chronic interstitial form of nephritis.

Pathological Anatomy.—In considering the morbid anatomy the terms "parenchymatous" and "interstitial" are preserved, with the understanding that they are not strictly applicable to any given case. Purely parenchymatous inflammation does not exist, nor does interstitial nephritis occur without any parenchymatous change, but one or the other almost always predominates. Diffuse nephritis is considered under the heading Parenchymatous Nephritis.

Parenchymatous degeneration and necrosis due to toxins or irritants of any kind may occasion disturbances of renal function entirely comparable to that caused by more definitely inflammatory lesions. Moreover, secondary changes in the connective tissues readily follow lesions of the parenchyma, as, on the other hand, interstitial processes are followed by parenchymatous degenerations. Thus it happens that purely parenchymatous or interstitial processes are exceptional.

Acute Parenchymatous Nephritis; Acute Bright's Disease

This results most frequently from infectious fevers and toxic agents. It is more common in young persons than in the old.

Acute Degenerative Nephritis.—The process in this condition may be almost purely parenchymatous in nature, and more nearly allied to pure degeneration than to inflammation. The epithelium of the tubules, especially in the convoluted portions, and to a certain extent also that covering the glomeruli, is swollen, cloudy, and considerably desquamated. Emigrated leukocytes, and occasionally red corpuscles, are found within the tubules and the capsule of the Malpighian bodies.

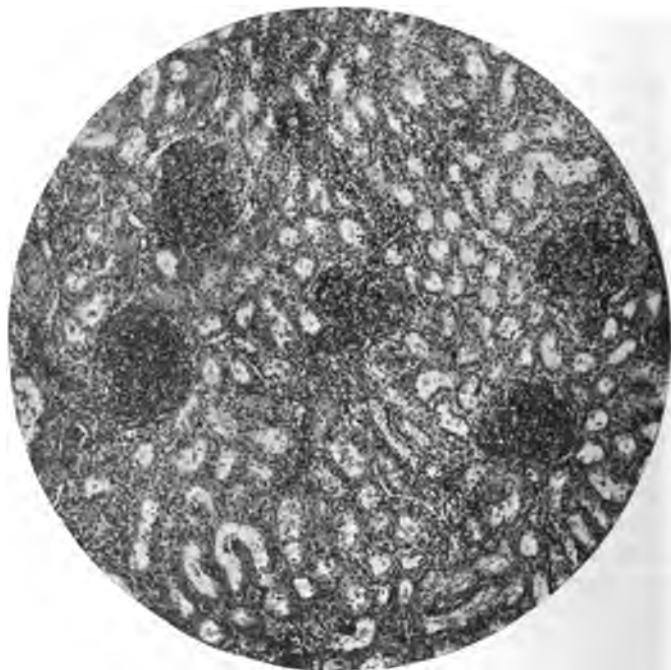


Fig. 331.—Acute glomerulonephritis.

The terms *acute catarrhal* or *desquamative nephritis* are more or less appropriate in such cases. The kidney is enlarged, somewhat swollen, and generally rather pale in color. The changes are most marked in the cortex, which is thicker than normal, and by its light color contrasts strongly with the pyramids. The capsule strips easily. In most cases the affection is one of slight severity.

Acute Glomerulonephritis.—In another group of cases, occurring most commonly in scarlet fever, the glomeruli are primarily attacked and most severely affected throughout the disease, but the general epithelial structures are also implicated. Such cases are designated *glomerulonephritis* (Fig. 331). The epithelium of Bowman's capsule may

or may not be involved; when it is, the cells are swollen and show hyaline change, and the capsular space contains an albuminous exudate. The Malpighian tuft is chiefly attacked; it is usually enlarged, and in the early stages shows an increase of cells, which may be so great as to completely obscure the capillaries. In the later stages the walls of the capillaries are thickened, the lobulation of the tuft is more distinct, and hyaline masses may be seen in some of the lobules. The increase of cells is chiefly due to proliferation of the vascular endothelium; however, polymorphonuclear leukocytes and lymphocytes may be present. Distinct hemorrhages into the capsular space and necrosis of the cells of the capsule and of the tuft sometimes occur.

Acute diffuse nephritis is the ordinary form of acute Bright's disease, and is the form in which either of the two preceding are prone



Fig. 332.—Acute diffuse nephritis, in which the interstitial infiltration is marked. Note degeneration of epithelium, increase of nuclei, and the swelling of glomerulus and its capsular lining.

to terminate. The kidney is enlarged, and sometimes congested and red in color; at other times it is light colored or even yellowish in consequence of the epithelial degeneration and the anemia caused by pressure due to the epithelial swelling. On section, the cortex is much increased in width, and when congestion exists it is more or less mottled, showing spots or streaks of reddish color, the intervening portions of the substance being grayish or yellowish in hue. In other cases the entire cortical substance is uniformly gray or yellow. The latter appearance

is commonly found in cases of considerable duration. In intense acute cases there may be punctate or linear hemorrhages, especially toward the surface of the organ, and the entire organ may be of a dark red color. In all cases the capsule strips easily from the underlying substance (Fig. 332).

Microscopically, the changes are most varied. In all cases there is more or less degeneration of the epithelium of the convoluted tubules and of that in the Malpighian bodies. In the earlier stages the cells become swollen and granular (cloudy swelling), while in advanced stages they may be filled with granules or droplets of fat (fatty degeneration). On the other hand, cases of great intensity may be marked from the very first by complete necrosis of the epithelial cells. Similar changes may be met with in the epithelium of the Malpighian bodies, and the latter may be converted into granular masses in which the capillary tufts are more or less obscured. Associated with these purely parenchymatous changes are found evidences of interstitial involvement in the presence of masses of round cells between the tubules and in the vicinity of the Malpighian bodies. Active proliferation of the connective tissues is also observed, though less markedly, in the same situations. Certain cases are distinguished by their special tendency to hemorrhagic extravasations into and around the tubules and into the Malpighian bodies. To such the name *acute hemorrhagic nephritis* is sometimes applied. This variety is especially common in intense septic or infectious cases, particularly such as are attended with minute embolism of the renal arterioles.

Acute Interstitial Nephritis

Non-suppurative acute interstitial nephritis may occur during the course of an infectious disease. The kidney is of a grayish opaque color, usually mottled with irregular hyperemic areas. On section, the normal markings are somewhat obliterated, and the contrast between the cortex and the pyramids is less marked. The interstitial change may be diffuse or focalized. It is usually most marked at the juncture of the cortex and medulla, in the region of a glomerulus or directly under the capsule. The cells found in these areas are proliferating connective-tissue cells, polymorphonuclear leukocytes, lymphocytes, or plasma-cells. Degeneration of the epithelial cells in the neighboring tubules may or may not be present. The blood-vessels of the kidney are always involved.

Suppurative nephritis may result from metastatic involvement of the kidneys in cases of general septicopyemia, from ascending inflammation in association with pyelitis, or from involvement of the kidney in cases of suppurative disease in the vicinity.

Embolic suppurative nephritis is characterized by the formation of small foci of suppuration in the substance of the organ, especially toward the periphery. These may occur as mere points of yellowish color, or they may be surrounded by a considerable zone of hemorrhagic infil-

tration. The surface of the organ may be studded with small elevated points, and as the process advances larger foci may form by confluence. Microscopically, the changes are found especially in the vicinity of the Malpighian bodies. Small capillaries are commonly found more or less obstructed with embolic plugs. Hemorrhagic extravasation is usually marked, and the accumulation of leukocytes leading to suppuration is the characteristic feature. Degenerative changes are seen in the epithelium of the vicinity, and, if the case has persisted for a certain length of time, the parenchymatous changes may be quite extensive.

In certain infectious fevers (pneumonia, typhoid fever, anthrax) micro-organisms escape from the blood through the kidneys. In such cases it is possible that the bacteria which have been excreted may cause infection in the lower parts of the uriniferous tubules. The occurrence of such nephritis is uncertain.

Suppurative pyelonephritis occurs in cases of suppurative pyelitis, especially in consequence of impaction of calculi in the pelvis. It is occasioned in most instances by ascending infection due to extension by surface continuity from lesions in an obstructed pelvis or ureter or along the lymphatics of their walls. When these passages are not obstructed the secondary lesions in all probability arise by hematogenic infection. When the inflammation has started in the bladder wall bilateral lesions are common, while only one kidney is affected should the infection begin in the ureter above its insertion in the vesical wall.

In the earlier stages small linear areas of light color are seen in the pyramids and medulla, running radially from the apex, and, microscopically, these are found to be uriniferous tubules infiltrated with pus-cells (Fig. 333). In the later stages these may run together, forming purulent collections of considerable size. The outer portions of the medulla and the cortex are only secondarily involved, and the suppurative areas here assume a more rounded shape. Pyelonephritis may terminate by rupture of the abscesses into the pelvis of the kidney and the discharge of the pus with the urine; by rupture on the surface of the kidney, causing *perinephric abscess*; or by inspissation and calcareous infiltration of the contents of the abscess. When discharge has taken place, or when inspissation occurs, induration and cicatrization of the diseased areas result. A considerable portion of the kidney may be thus converted into scar tissue.

Suppurative nephritis, following suppuration around the kidney, leads to the formation of superficial abscesses and erosions.



Fig. 333.—Pyelonephritis, showing lines of ascending suppuration (Kaufmann).

CHRONIC NEPHRITIS

Chronic nephritis presents itself in varieties allied to the acute forms, and we may distinguish chronic parenchymatous and chronic interstitial nephritis. The former is practically always a diffuse process, presenting no such limitations to the epithelium of the tubules or to the glomeruli as are witnessed in the acute disease. Chronic interstitial nephritis is characterized mainly by hyperplasia of the connective tissue.

CHRONIC PARENCHYMATOUS NEPHRITIS

Chronic parenchymatous nephritis in most cases results from acute attacks which have become chronic by continuation or repetition. It occurs after various infectious diseases, in consequence of alcoholism, or in an obscure manner, auto-intoxication probably accounting for some of the last group of cases.

Pathological Anatomy.—The kidney is usually enlarged, and on section the cortical substance is often increased in width. The color is most frequently grayish or yellowish in consequence of the disease of the epithelium and of the anemia caused by the swelling of the cells. The pyramids may be quite red and swollen, or may be compressed and light in color. The capsule strips easily, and the substance of the organ is only moderately firm; sometimes, indeed, it is quite soft. To this form of chronic parenchymatous nephritis the term *large white kidney* is often applied. In other cases the substance of the organ may be quite red in color, or may be mottled, light areas of yellowish or gray color alternating with congested portions. In such cases careful examination may show punctate or linear extravasations of blood, and the term *chronic hemorrhagic nephritis* is not inappropriate. The kidney is enlarged, as in the first variety, the cortex thick, and the capsule easily removed. In either case small cysts may form in the substance of the organ or upon the surface by distention of the convoluted tubules or capsules of Bowman (Fig. 334).

In the later stages of chronic parenchymatous nephritis the degenerative processes in the epithelium become pronounced, and the organ may grow progressively lighter in color and more fatty in appearance, with streaks of fat running up between the striæ from the pelvis. Some investigators would view the pallor of the large white kidney as due to protagon in a finely granular state in the renal cells, and not to fat. At the same time interstitial processes associate themselves, and the substance of the organ becomes more firm and the kidney may be reduced in size. Attachments are formed between the substance and the capsule, which is no longer removable without laceration of the underlying substance. This terminal form of chronic parenchymatous nephritis has been designated as *fatty contracting kidney*, or as *secondary interstitial nephritis*, according to the amount of fatty parenchymatous change or of interstitial overgrowth present in the individual case (see p. 729).

Microscopically, chronic parenchymatous nephritis is marked by striking degenerative changes in the epithelial cells of the convoluted tubules, and to a less extent in those lining the capsule of Bowman and covering the Malpighian tufts (Fig. 335). The epithelium of the tubules is at first swollen and finely granular (cloudy swelling), the



Fig. 334.—Chronic parenchymatous nephritis with large and small retention cysts.

nucleus being obscured and the cells oftentimes becoming fused. In moderately advanced cases it is rather characteristic to see a low even lining of fused epithelia, sometimes with a rather frayed edge toward the lumen (Fig. 336). In the more advanced stages of the process marked fatty degeneration of the cells is discovered, and they may break down

completely, so that the lumen of the tubule is filled with fatty and granular detritus (Fig. 336). Extravasations of leukocytes or of red blood-

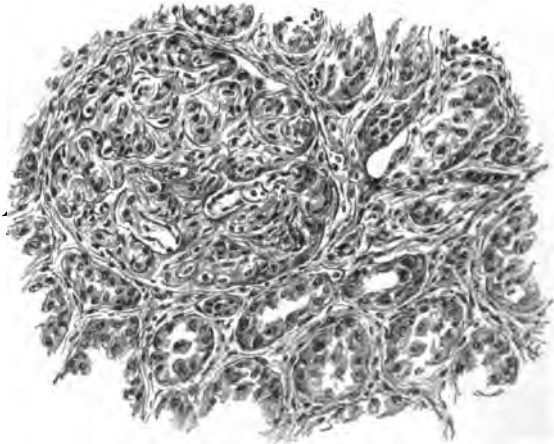


Fig. 335.—Chronic parenchymatous nephritis, showing marked involvement of the Malpighian body and considerable interstitial change.

corpuscles may take place, especially in the form known as *hemorrhagic nephritis*. Many of the tubules may be filled with tube-casts of hyaline

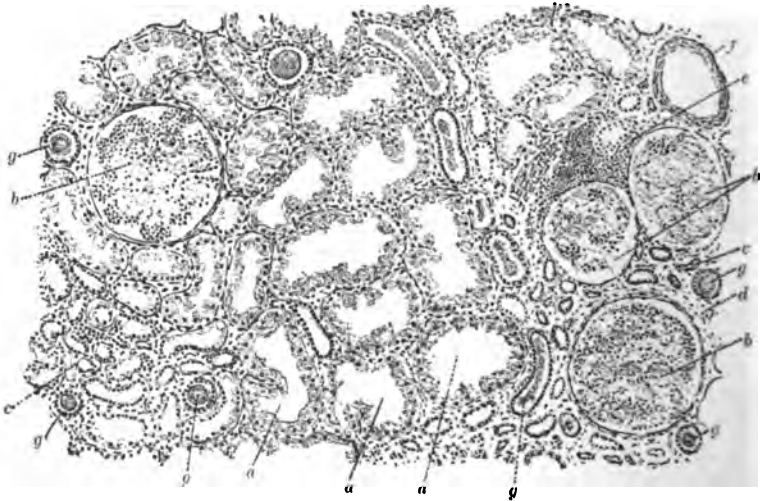


Fig. 336.—Chronic parenchymatous nephritis: *a, a, a*, Convoluted tubules with cloudy swelling of the epithelium; *b, b, b*, glomeruli, more or less degenerated; *c, c*, atrophic tubules; *d*, sclerotic interstitial tissue; *e*, round-cell infiltration; *f*, blood-vessel; *g, g, g, g, g*, tube-casts in tubules (Kaufmann).

or, more frequently, of granular appearance. The Malpighian bodies are usually simultaneously, though perhaps less markedly, affected.

The epithelium in the latter is proliferated and degenerated, and the vascular tuft may present considerable hyaline degeneration. In the hemorrhagic variety the capsular space may be completely filled with extravasated blood. Side by side with these parenchymatous changes may be seen changes in the interstitial tissues. Notably, there are proliferation and thickening of the capsule of Bowman and of the connective tissues between the tubules. Sometimes cases are seen in which connective-tissue increase about the capsule of Bowman is prominent, but in this form of nephritis the fibrous tissue is more diffuse than in the primary chronic interstitial form. In advanced stages these interstitial changes are always present, and in those cases known as secondary interstitial nephritis the connective-tissue hyperplasia is the predominating condition. The walls of the small blood-vessels of the kidney are usually thickened by hyperplasia.

CHRONIC INTERSTITIAL NEPHRITIS

Chronic interstitial nephritis leads to the formation of a contracted kidney. This may be a secondary form of nephritis following passive congestion or chronic parenchymatous nephritis, or it may be primary, when it is often associated with diffuse arteriosclerosis.

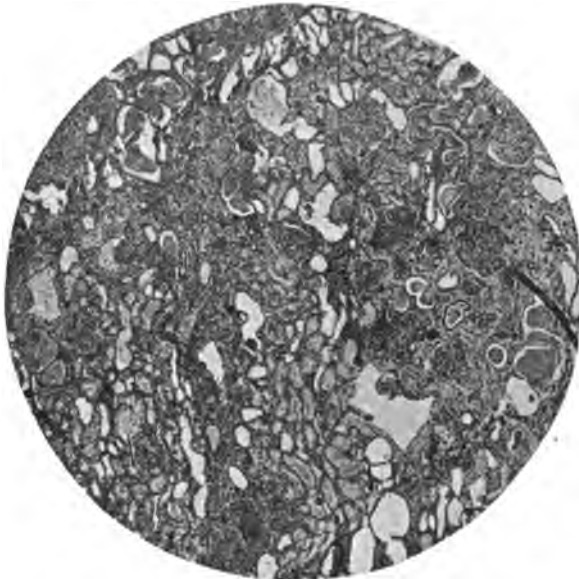


Fig. 337.—Chronic interstitial nephritis, showing small cystic dilatations of tubules.

Secondary chronic interstitial nephritis is the terminal stage of certain cases of chronic parenchymatous nephritis, and results from a continuous hyperplasia of the interstitial tissues, with degeneration and atrophy of the parenchyma. The organ is reduced in size, and may be

quite irregular upon the surface, the irregularity taking the form of large depressions or of fine granulations. The capsule strips with difficulty, portions of the kidney substance remaining attached. On section, the kidney is found to be firmer than normal, and is of light color, often yellowish (fatty) in hue. The cortex may be nearly the normal thickness or may be considerably reduced. The small blood-vessels of the substance of the organ may be gaping and visibly sclerotic.

Microscopically, the epithelium of the tubules is granular, fatty, or atrophic, and the cells are found detached in great numbers and occupying the lumen of the tubules. The tubules themselves may be compressed by surrounding interstitial overgrowth, or may be distended even to the formation of cystic dilatations (Fig. 337). The capsule of

Bowman is greatly thickened, and the Malpighian bodies may be much distorted and compressed.

Primary Chronic Interstitial Nephritis; Red Granular Kidney; Arteriosclerotic Nephritis; Gouty Nephritis.—All of these terms have been applied to a form of interstitial nephritis probably produced by irritants conveyed through the circulation. As has been suggested on p. 721, in discussing the etiology of nephritis, repeated insults to the parenchyma, or congestion and edema of the supporting tissue by circulating poisons is responded to by nature in the form of connective-tissue formation. It occurs in consequence of alcoholism, syphilis, gout, chronic plumbism, chronic cachexias of other kinds, and various forms of

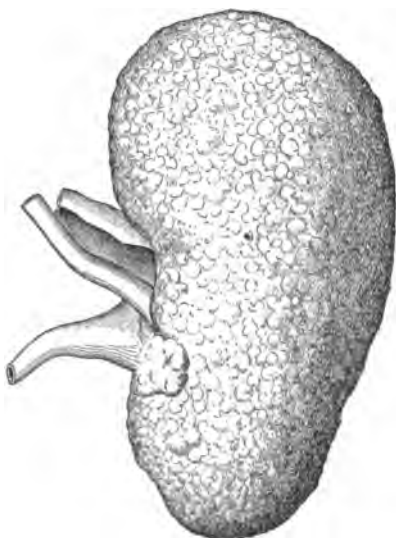


Fig. 338.—Chronic interstitial nephritis: granular kidney (Orth).

subinfection, or as a part of the effects of focal infection. It is not rarely associated with diffuse arteriosclerosis. A certain amount of interstitial nephritis of this variety is a natural lesion of old age.

Pathological Anatomy.—The kidney is usually decreased in size, and sometimes may be very much contracted. In other cases the reduction in the dimensions is inconsiderable, and the size may even be increased. The surface is irregular, and, on removal of the capsule, is found to be finely granular or irregularly lobulated (Fig. 338). The capsule itself strips with difficulty. Small cysts may be seen upon the surface. On section, the substance is firm, and may sometimes be almost cartilaginous in consistence. The cortex is narrow, often being reduced to one-quarter or one-sixth its normal width, while the pyramids may be increased in size or contracted like the cortex, and not rarely show dense white sclerotic tissue radiating from the apices. In gouty

cases deposits of urates may be observed in the same situation. The color of the kidney varies, but is usually grayish brown or gray. The blood-vessels in the substance of the organ are usually gaping and their walls visibly thickened.

Microscopically, chronic interstitial nephritis is characterized by great hyperplasia of the connective tissue surrounding the Malpighian

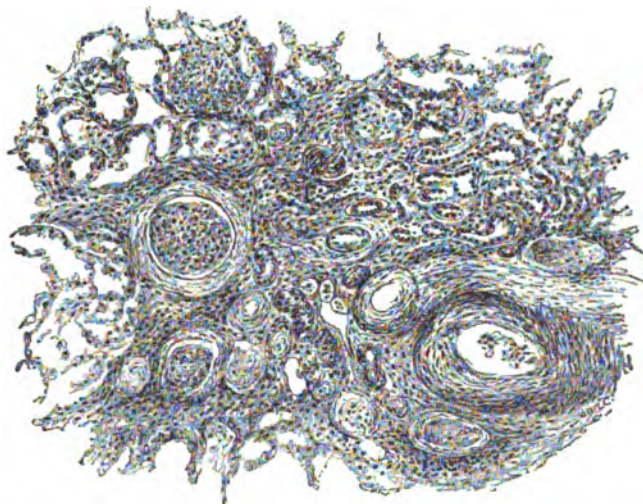


Fig. 339.—Chronic interstitial nephritis: great increase of connective tissue around the glomeruli, renal tubules, and blood-vessels.

bodies and the convoluted tubules, and by hyperplasia of the walls of the blood-vessels (Fig. 339). The overgrowth of connective tissue may be irregular in its distribution and may vary greatly in amount. In beginning cases there is only moderate thickening of the capsules of Bowman and of the intertubular tissues and walls of the blood-vessels. In ordinary cases fibrous thickening of the Malpighian capsules, with new formed connective tissue consisting of young connective-tissue cells and round infiltration cells between the tubules and sclerotic thickening of the blood-vessels, constitute the striking microscopical features (Fig. 340). In the most pronounced cases the kidney substance is almost wholly transformed into fibrous tissue of dense sclerotic character. The epithelium undergoes progressive atrophy, the cells shrinking in size and becoming granular and loosened from the basement-membrane. Hyaline or granular tube-casts may be found within

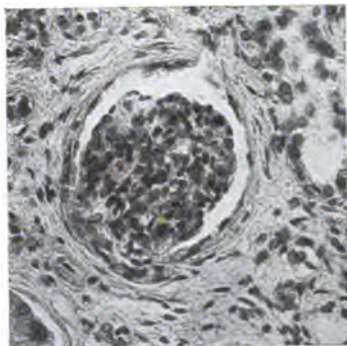


Fig. 340.—Chronic interstitial nephritis (from a photograph by Dr. Wm. M. Gray).

the tubules, and the latter are compressed by contraction of the new formed connective tissue, the parts distal to the constriction being distended with secretion or seemingly dilated by the disappearance of the epithelium.

The arteriosclerotic kidney, while in the main closely like the group description just given; presents a few features by which it can be recognized pathologically. It is a small, hard, granular, reddish or red-gray organ, usually without cysts; it has an adherent capsule, and upon section shows a narrowing of both cortex and medulla, prominent vessels with wide walls, and distinct glomeruli. Microscopically, the connective-tissue increase is greatest in the vicinity of vessels and in their walls, and it is only late that glomeruli and tubules are wholly obliterated. The tufts may show hyaline degeneration by reason of the interference with their blood-supply. Arteriosclerosis being an irregular process, it follows that not all sections of the kidney will be affected the same way; while in chronic nephritis of primary character or that succeeding an acute diffuse affection pathological alterations are more evenly distributed through the organ.

Pathological Physiology of Nephritis.—The effect of acute or chronic nephritis varies greatly in individual cases. Profound systemic disturbances in acute cases are doubtless often the result of the action of toxic substances which caused the nephritis, rather than of the disease of the kidneys itself. In uncomplicated cases of acute or chronic nephritis the influence upon the general metabolism is seemingly slight. Investigations have not as yet shown any decided increase in the metabolic consumption of the tissues, and no specific disturbances of metabolism of any sort have been discovered. It is very likely, however, that extensive disease of the kidneys does exercise some influence, since these organs undoubtedly have actual glandular functions and are not merely passive agents for the filtration of the blood and the excretion of urine. The peculiar intoxication which occurs in nephritis, and to which the name uremia (*q. v.*) is applied, has received no satisfactory explanation. It is probable that substances normally excreted in the urine are retained in the blood and accumulate to such an extent that intoxication results. It is also likely that substances which are normally elaborated by the kidneys and excreted in altered forms remain in the blood and occasion disturbances. Marked retention of non-protein nitrogen is found in nephritics and especially in uremia. During the progress of uremia there seems undoubtedly to be active tissue consumption, but accurate studies are wanting. Excretion of sodium chlorid is decidedly diminished in nephritics, and the retention of this salt is a factor in the development of the edema of renal disease.

Gastro-intestinal symptoms are frequent in renal disease. In a notable proportion of cases the gastric secretion has been found deficient, and this may account for some of the disturbances. Putrefactive processes in the intestines have also been demonstrated in some cases, being evidenced by the increased quantity of ethereal sulphates in the urine. In the later stages of nephritis, and especially in uremia, severe gas-

tro-intestinal disorders sometimes develop. These have been explained by the assumption that urea is excreted through the gastro-intestinal mucous membrane, and undergoes ammoniacal decomposition within the digestive tract. The ammonia formed by this decomposition is supposed to be the immediate cause of the gastro-intestinal disturbance.

The **urine in nephritis** is of the greatest interest. In acute cases, and sometimes in chronic forms, it suffers notable change of appearance by admixture of blood. In other instances the color and physical properties are to a large extent dependent upon the amount of urine excreted. As a rule, the quantity of urine is decreased in nephritis. The nitrogenous elimination is of particular interest. In acute cases, in which the quantity of urine is greatly deficient, there is undoubtedly an insufficient excretion of nitrogen in the urine; subsequently the nitrogenous element may be excreted in increased quantities. In acute nephritis without marked diminution in the quantity of urine the nitrogenous elimination may remain satisfactory. In chronic nephritis the elimination of nitrogen in the urine may be reduced, both in the parenchymatous and interstitial forms of the disease. Nitrogen retention is not invariable, and from time to time periods of increased elimination may occur. The amount of urea is very commonly decreased; in part this may be compensated for by increased elimination through the skin and intestines. The uric acid is usually decreased in quantity, but may be entirely normal in any form of nephritis, and may in some instances be temporarily increased. Ammonia is present in normal quantities; during uremia it may be increased. Xanthin may be present in increased quantities, and creatinin is reduced in quantity.

The urine in nephritis presents two striking peculiarities: the presence of albumin, discoverable by chemical examination, and the presence of tube-casts. Albuminuria is an almost constant symptom, though occasionally, in chronic interstitial nephritis, the amount may be so small that it is not detected by the cruder tests. The more delicate methods will probably detect albumin in every case. Serum-albumin is the more important form, but globulin occurs in small amounts in every case when albumin is excreted. In hemorrhagic forms of acute or chronic nephritis and in cases complicated by amyloid degeneration, globulin may be found in considerable quantity.

Albumin is excreted by both the glomeruli and the tubules, but the former is by far the more important. Damaged epithelium will permit albumin to pass; it is not necessary that the cells be desquamated.

The **tube-casts** met with in nephritis are casts formed within the convoluted tubules, or more rarely in other parts, and are composed of albuminoid substances and possibly sometimes of fibrin. They are formed partly of materials which have accumulated in the tubules by exudation, partly of the granular detritus of the degenerated epithelium, or of red and white blood-corpuscles. We may distinguish a number of varieties, viz., hyaline, cellular, crystalline, and granular casts and cylindroids.

Hyaline casts are clear, rounded bodies having a diameter of from 0.01 to 0.03 mm. and a variable length. Sometimes they are quite short; at other times they extend across several fields of the microscope. They may be straight, or spiral or contorted. Sometimes they are so transparent and light colored that they are scarcely visible, or, on the other hand, they may be of a denser structure and less transparent. Hyaline casts are frequently met with in simple congestion of the kidney and in icterus unassociated with discoverable nephritis. They are most abundant in acute parenchymatous nephritis, but are met with also in chronic parenchymatous and interstitial nephritis. A form of hyaline cast known as the *waxy cast* is met with, sometimes in acute, but more commonly in chronic, nephritis (Fig. 341). It is distinguished by the moulded, wax-like appearance and by its apparent rigidity.

Cellular Casts.—The most frequent form is that in which the surface of a hyaline or granular cast is covered with epithelial cells that

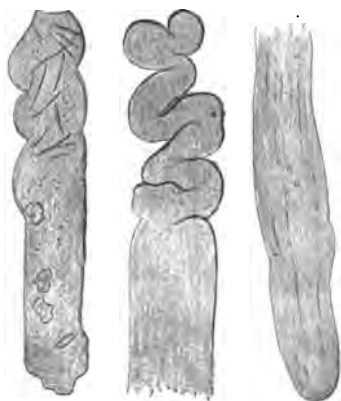


Fig. 341.—Waxy hyaline casts.

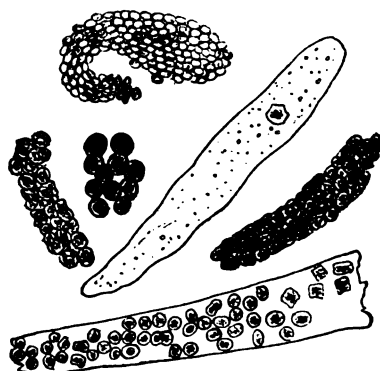


Fig. 342.—Blood-casts, composed wholly of red or white corpuscles, or hyaline substance covered with blood-corpuscles.

have detached themselves from the tubules. The entire surface may be covered, or there may be but a few cells here and there. This form is found especially in acute parenchymatous nephritis. *Leukocytic casts* are moulds of the tubules composed of masses of leukocytes. They are found especially in purulent pyelonephritis. Occasionally leukocytes are found upon the surface of other casts. *Blood-casts*, composed of red blood-corpuscles or of blood-pigment formed by disintegrated red corpuscles, are frequently observed in acute and chronic hemorrhagic nephritis (Fig. 342).

Crystalline Casts.—Moulds of the tubules, composed of uric acid or oxalate of lime, are sometimes observed in chronic nephritis, when there is a tendency to the deposition of the crystals named (Fig. 343, A). Similar formations may be met with in the urine of the newborn independently of nephritis (see page 740).

Granular casts may be light or dark, according to the amount and character of the granular material. They are composed of substances derived from broken-down epithelial cells, and are especially common in chronic nephritis, though they may occur in quite acute cases. Sometimes, instead of granular matter, the débris of the epithelial cells occurs as oil drops, and the term *fatty casts* is appropriately applied

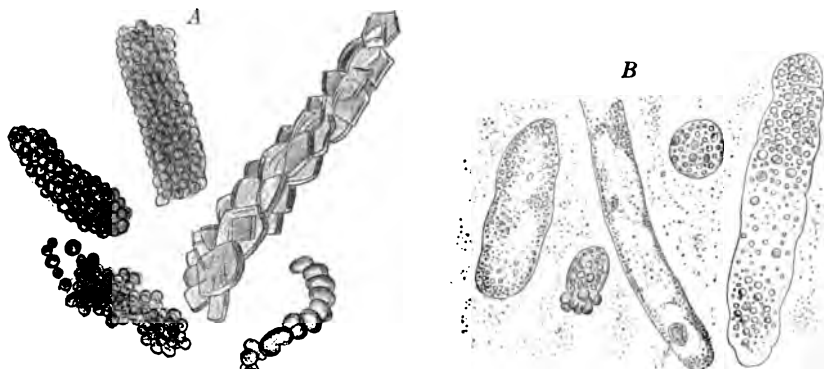


Fig. 343.—A, Tube-casts, composed of uric-acid crystals. B, Granular and fatty casts and two compound granular cells.

(Fig. 343, B). The diameter and length of granular casts vary considerably. As a rule, the diameter is about the same as that of the hyaline casts, but the length is rarely as great.

Cylindroids are formations resembling casts more or less closely. Sometimes they appear as thread-like formations, rounded or flat, and occurring singly or in twisted bunches. In other cases they may be quite similar to hyaline casts, though distinguished by a long, tapering end or tail (Fig. 344). Cylindroids occur in conditions of renal irritation not sufficient to constitute nephritis, as well as in cases of genuine nephritis. They are also supposed to be produced in the tubular glands of other parts of the genito-urinary tract, as in the glands of Cowper.

Other Constituents of the Urine.—Various cellular constituents are found in nephritis. In acute and in chronic hemorrhagic nephritis white and red blood-corpuscles are frequently observed; and epithelial cells are more or less abundant in all forms of parenchymatous nephritis. In the acute varieties swollen and granular rounded cells are observed; in the more chronic forms, particularly when fatty degeneration is pronounced, epithelial cells or leukocytes densely filled with dark granular or globular fat are conspicuous. The term *compound granule cell* has been applied to these cells.

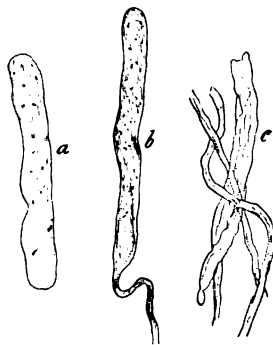


Fig. 344.—Cylindroids: a and b, Cast-like forms; c, filamentous forms.

Results of Nephritis.—Nephritis leads to notable changes in the entire organism, and particularly in the vascular system.

Cardiac Changes.—In acute nephritis there may be associated acute degenerative or inflammatory lesions of the heart muscle, and cardiac dilatation may occur. These, however, are usually results of the infectious or toxic cause underlying the nephritis, rather than results of the nephritis itself. When parenchymatous nephritis becomes subacute or chronic, hypertrophy of the heart (notably of the left ventricle) takes place, and this may reach extreme proportions in chronic interstitial nephritis. The cause of the hypertrophy of the heart has occasioned much controversy. It seems likely that it is in large part the result of irritation and overstimulation of the heart muscle by substances retained in the blood, instead of being excreted. These retained substances seem to have the effect of raising the vascular pressure, a factor of undoubted importance in throwing extra work on the heart. The obstruction to the circulation occasioned by thickening of the walls of the renal vessels is of little moment; and the theory that the cardiac hypertrophy is due to a hydremic condition and increased quantity of blood, in consequence of retention of water in the system, is negated by the fact that such hydremic excess of blood is certainly absent in many cases. Associated arteriosclerosis is undoubtedly one of the important factors in the production of cardiac hypertrophy.

Arteriosclerosis.—The arteries are frequently sclerotic in cases of chronic nephritis. In part this is due to the direct action of toxic products of improper metabolism occurring in Bright's disease; in part it is a coincidental or an antecedent condition.

Acute inflammatory lesions of the serous membranes, and to a less extent of the mucous membranes, sometimes occur in Bright's disease. Acute endocarditis, acute pericarditis, and pleurisy are the most frequent conditions. Of the inflammatory conditions of the mucous membranes, tonsillitis and pharyngitis are not infrequent. Enteritis, even of ulcerative type, may occur, especially in chronic nephritis. This, in part, seems to result from vicarious excretion of irritant matters from the intestinal mucosa.

Edema, or dropsy, is a frequent manifestation of nephritis. It is most frequent in the parenchymatous forms, particularly in such as occasion changes in the glomeruli and other vascular portions of the kidney. In chronic interstitial nephritis dropsy is rarely observed until the late stages, when manifest arterial disease and failing circulation from cardiac weakness have supervened. The edema usually begins in the loose subcutaneous tissues of the eyelids and hands, but extends to all parts of the body, causing anasarca. Internal edema, and especially edema of the lungs, may be met with.

Uremia is the name applied to certain clinical manifestations probably caused by the retention of toxic substances in the blood which ordinarily are excreted with the urine. The nature of the substance or substances in question remains obscure. Neither urea, potassium or ammonium salts, uric acid, nor various other constituents of the urine

alone produce uremic manifestations, though the injection into animals of some of these may cause toxic symptoms, such as convulsions or coma. It may be that uremia is caused by the conjoined action of a number of such toxic bodies, but it is not improbable that the poisons are substances as yet undiscovered. The theory that uremia is due to edema or anemia of the brain may be definitely abandoned. The view has been expressed that toxic substances are liberated by the renal cells as a consequence of their degeneration, and that these "nephrotoxins" are concerned in uremia. This theory is still entirely speculative.

ATROPHY AND HYPERTROPHY

Atrophy of the kidney may be congenital (hypoplasia), or may occur in old age (senile atrophy). In the latter case (sometimes called "senile nephritis") the kidney is small, hard, and usually darker in color than normal. The irregular atrophy of the parenchyma leads to irregularities upon the surface of the organ. The capsule may be thickened, and not rarely the perirenal fat is abundant, and considerable fatty deposit occurs beneath the mucous membrane of the pelvis.

Microscopically, the renal cells are small in size, somewhat dark and granular. They may disappear entirely from the tubules in places, and the intertubular tissue and the basement-membrane are correspondingly thickened. The Malpighian bodies may be converted into contracted fibrous areas. In some cases the interstitial processes become so pronounced that the kidney presents the picture of interstitial nephritis. These cases are particularly met with in persons of advanced years having arteriosclerosis. (See Chronic Interstitial Nephritis.)

Hypertrophy may affect one kidney when its fellow is congenitally wanting, has become diseased, or has been removed. Under these circumstances the remaining or healthy organ sometimes undergoes considerable hypertrophy. The appearance is that of a much enlarged but otherwise normal kidney.

Microscopically, there may be simply increase of the size of the tubules, or in cases in which the compensatory hypertrophy has begun before the completion of development there may be actual increase in the number of tubules and Malpighian bodies.

DEGENERATIONS

Parenchymatous degeneration, or cloudy swelling, occurs in the kidneys in consequence of the action of various poisons, infectious or chemical. It is met with in practically all cases of diphtheria, scarlet fever, and cholera, and less commonly in many other infectious diseases. Among the poisons the various parenchyma poisons (*q. v.*, Part I) are all capable of attacking the kidney and producing cloudy swelling. In case of either toxic or infectious degenerations, however, the process is prone to become more serious and to terminate in acute parenchymatous nephritis. No sharp dividing-line can be drawn between the two conditions.

The kidney is somewhat increased in size, is softer than normal, and, on section, the cortex is yellowish or of light grayish color (Fig. 345). The Malpighian bodies may be prominent as red spots lying in the light-colored renal tissue. The pyramids are often congested and contrast strongly with the cortical substance.

Microscopically, fine granulation of the cells of the convoluted or other tubules is the striking feature. The nuclei of the cells are obscured, and at times all of the cells of the tubules apparently become fused. Exudative changes and hyperplasia of the interstitial tissues are wanting in a purely degenerative condition. Frequently the kidney is restored to the normal condition, but, on the other hand, acute Bright's disease or fatty degeneration may ensue.

Fatty Degeneration.—This occurs in consequence of the last-described condition, or independently in consequence of general anemia



Fig. 345.—Parenchymatous degeneration of the kidney, from a case of cholera (modified from Kast and Rumpel).

and systemic disorders, as in progressive pernicious anemia and tuberculosis. Fatty degeneration of the kidney frequently occurs in the course of pregnancy, when it is due to disturbance of the circulation in the kidneys or possibly to obstruction of the ureters. In these cases the process usually advances to the condition of diffuse nephritis.

In pure fatty degeneration the kidney is about the normal size, or often smaller than normal; is soft; and, on section, the cortex has about the normal width. The color is uniformly yellowish or mottled, certain areas being yellowish in color and others normal or perhaps hyperemic. Usually the surface of the kidney is smooth, but sometimes localized spots of degeneration may become depressed and give rise to irregularities.

Microscopically, the epithelial cells are granular or filled with oil-drops (Fig. 346). Not rarely the cells are loosened and lie free within the lumen of the tubules. The basement-membrane and interstitial tissues may be somewhat thickened, either apparently or actually.

Fatty infiltration is an unimportant condition. In the atrophic kidneys of old age and in the contracted kidneys of chronic nephritis fatty infiltration of the areolar tissue beneath the mucosa of the pelvis is

frequently observed. Fatty infiltration of the epithelial cells may occur under normal conditions, or in cases in which the blood is surcharged with fat (*lipemia*) and in which the kidneys are actively engaged in its excretion. Fatty infiltration of the perirenal cellular tissues occurs in general obesity, and sometimes as a localized affection in cases of advanced renal disease, particularly atrophy.

Calcification may occur in diseased areas of the kidneys, as in degenerated and fibrosed areas, in old infarcts, and the like. Occasionally calcification occurs in the epithelial cells themselves, particularly in such as have undergone necrosis. This is particularly marked in certain poisonings (*e. g.*, mercuric-chlorid-poisoning). Calcium salts are sometimes deposited in infarct arrangement in certain diseases of the skeleton, notably osteomalacia. This is a part of the so-called calcium metastasis.



Fig. 346.—Fatty degeneration of the epithelium of the tubules, stained with osmic acid (Simmonds).

Calcareous bodies in the cortex of the kidney are not infrequent. They are due to calcification of little cysts springing from the uriniferous tubules or Malpighian bodies.

Glycogenic infiltration of the kidneys occurs in diabetes. It affects the epithelial cells, particularly those in the portions of the organ lying between the medulla and the cortex. The kidney is usually increased in size, the cortex broader than normal, and the consistency increased. The substance may be lighter colored and of homogeneous appearance. Microscopically, the epithelial cells, particularly those of the tubes of Henle, are found to be altered in character, the normal granular condition of the protoplasm having disappeared. The glycogenic nature of the infiltrating substances is recognized by the dark-brown color obtained by staining fresh sections with iodine.

Amyloid infiltration occurs in the kidneys under the same conditions as in the liver and spleen. It is most frequent in cases of chronic tuberculosis of the lungs, and occurs in cases of long-standing suppu-

tion connected with bone, in syphilis, and as a result of other cachexias. The kidney is enlarged, sometimes to twice its normal bulk, is harder than normal, and, on section, the substance is found light grayish in color. It may be uniformly grayish or waxy; or, on the other hand, it may be mottled, grayish areas alternating with portions of yellow color, the latter being due to fatty degeneration. Amyloid deposit begins in the small blood-vessels, particularly those of the Malpighian tufts, and spreads to the connective tissues of the organ, but does not involve the epithelium.

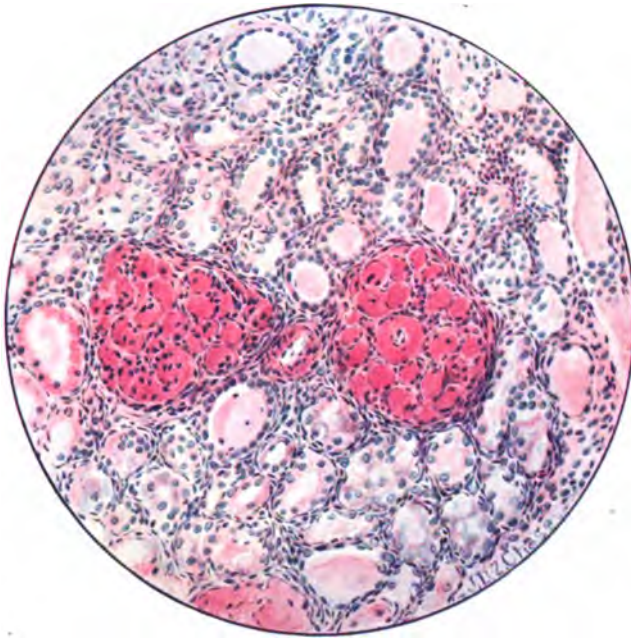
Microscopically, the glomeruli may present spots of hyaline or homogeneous appearance in which the capillaries seem completely disorganized, and the entire glomerulus may be transformed into a transparent or translucent mass (Plate 13). The capsule is thickened and oftentimes simultaneously diseased. The tubules habitually contain hyaline casts. The organ becomes more or less anemic from obstruction of the capillaries, and sooner or later fatty degeneration of the epithelial cells takes place. Inflammatory processes are usually wanting, but nephritis may become associated with amyloid degeneration, and the latter process may occur in kidneys primarily the seat of nephritis. Litten finds that the glomeruli are not always the first part affected; neither is the muscularis of blood-vessels always the starting-point. The adventitia or intima may be first affected. He distinguishes the following varieties of amyloid kidney: (a) Pure amyloid kidney with amyloid change of the blood-vessels and with or without fatty change in the epithelium. Macroscopically, the kidney may seem to be normal, but the iodine reaction indicates its true condition. (b) Large white amyloid kidney. This is the commonest form, and consists of amyloid degeneration plus chronic parenchymatous nephritis. (c) Amyloid contracted kidney is comparatively rare, and a very rare form is (d), the association of acute nephritis with amyloid change in the blood-vessels.

The urine in amyloid disease is albuminous and scanty; the proportion of serum-globulin is excessive. Not rarely it contains hyaline casts which respond more or less distinctly to the color-tests for amyloid substance, but these are not diagnostic, and it is doubtful whether they are, in reality, composed of amyloid material.

CONCRETIONS IN THE URINIFEROUS TUBULES

Various calcareous concretions, or "infarcts," occur in the uriniferous tubules, particularly in the large collecting tubules near their termination at the apex of the pyramids. Collections of urates, particularly urate of ammonium, are frequently seen in the form of radiating lines of light grayish, yellowish, or reddish color, marking the pyramids near the apices in newborn infants. These consist of crystalline concretions filling the large uriniferous tubules, and have been considered as a valuable medicolegal indication that the infant had breathed. They are not, however, sufficient proof. Sometimes the concretions are passed with the urine, and are discovered as large casts of conglomerated crystals. Less frequently other forms of crystals are met with in the infarcts of

PLATE 13



Amyloid infiltration of capillary walls in kidney glomerulus.

the newborn. Similar concretions occur in gouty individuals, particularly in aged persons, and calcium salts may be deposited when the blood is surcharged with them in consequence of diseases of the bones. Triple phosphates may be found as a consequence of obstruction of the urinary passages and stagnation of urine.

Concretions composed of bilirubin may be formed in extreme jaundice, and particularly in the jaundice of the newborn. Infarcts composed of hemoglobin may be seen in cases of hemoglobinuria due to infectious and toxic causes.

INFECTIOUS DISEASES

Tuberculosis may occur in the kidney in the form of minute, grayish-white miliary tubercles as part of a general hematogenous tuberculosis. A second form, which is also hematogenic, is known as *chronic local tuberculosis*. In this form the substance of the kidney near the cortex, or sometimes that adjacent to the pelvis, is occupied by masses of cheesy tuberculous tissue, and there may be secondary miliary tuberculosis near by. Softening is prone to occur, and the tuberculous focus may discharge into the pelvis of the kidney, leaving a necrotic cavity. The entire organ may be honey-combed with cavities. Tuberculosis of the kidney may also result from ascending infection, being secondary to tuberculosis of the seminal vesicles, of the bladder, of the ureters, and of the pelvis of the kidney. The process first involves the discharging tubules at the apices of the pyramids and spreads outward toward the cortex. Cheesy foci are formed, which may soften and discharge into the pelvis, as in the case of chronic local tuberculosis of the kidney. It is difficult to determine whether tuberculosis of the kidneys is more frequently the result of urogenital tuberculosis primarily affecting the parts below, or the cause of the latter. Primary affection of the kidney is certainly more common than many have been disposed to admit.

Syphilis.—In the earlier stages of syphilis there may possibly be acute nephritis similar to that of other infectious diseases. Syphilis of long duration may lead to amyloid degeneration of the kidney or to chronic interstitial nephritis. Thickening of the blood-vessels is conspicuous. In the latter case contractions of fibrous tissue leading to marked lobulation are rather characteristic. Syphilitic gummata are rare, but have been met with, and in their healing lead to marked scar formation.

Lesions of leprosy, actinomycosis, and glanders have been observed.

TUMORS

Fibromata and **lipomata** may occasionally be met with in the kidney in the form of small rounded nodules. In association with calculous pyelitis and other conditions of the kidney leading to atrophy, the fatty tissue surrounding the kidney may be increased to such an extent as to constitute practically a fatty tumor.

Leiomyoma is an occasional growth of the kidney.

The most important tumors of the kidney are classified nowadays under the **teratomata**; they are the *hypernephroma* or Grawitz tumor, and the *adenosarcoma* or Wilm's tumor.

Hypernephroma.—Under the name of *struma aberrata suprarenalis* or *hypernephroma*, has been described a form of tumor of the kidney

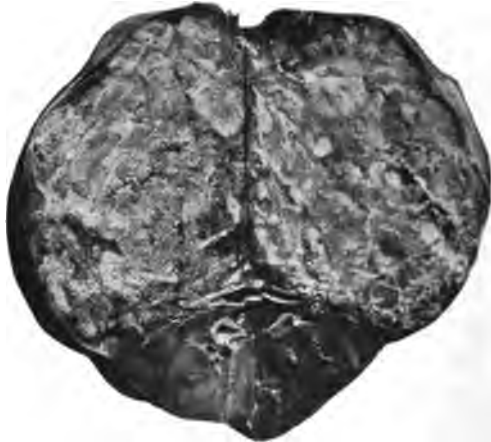


Fig. 347.—Hypernephroma of kidney, showing destruction of most of the kidney substance. The tumor was yellow in color (from a specimen in the collection of Dr. Allen J. Smith).

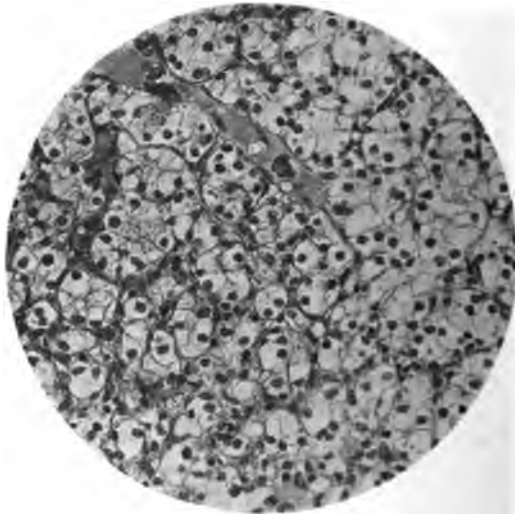


Fig. 348.—Finer structure of the adenomatous form of hypernephroma.

which results (Grawitz) from splitting off of a remnant of the suprarenal capsule and its incorporation in the kidney, where it subsequently grows (Figs. 347, 348). Wilson would explain these tumors as remains of the primary kidney tubules, nephrogenic tissue in the Wolffian duct.

Dunn has found abnormal epithelial structures frequently in the kidney. These consist of suprarenal rests, adenopapillary tissue, and papilliferous cysts. This finding would help explain the variations seen in Grawitz's hypernephroma, since some are distinctly adrenal in character, while others show architectural features of carcinomata. The tumor presents the appearance of a small lipomatous *yellow* growth beneath the capsule of the kidney, or, more rarely, it may attain considerable size. Histologically, it consists of epithelial cells arranged in tubules similar to those of the cortical portion of the suprarenal capsule. These undergo considerable fatty infiltration, and almost the entire tumor may be fatty. Occasionally active proliferative changes occur in the epithelium, and a malignant character is assumed.

Hypernephroma is very prone to invade the renal vein by extension. Epinephrin does not occur in hypernephromata, a fact consistent with the theory that they arise from tissue related to the suprarenal cortex.

Sarcoma of the kidney is a frequent malignant tumor. It may occur congenitally, usually as a teratoma or a mixed tumor, or as a simple



Fig. 349.—Primary sarcoma of the kidney.

form in later life. The size and general appearance vary considerably, but for the most part the structure is soft and *grayish* or sometimes *quite red*. Extravasations of blood or hemorrhages into the tumor are not uncommon. There may be a distinct capsule or the growth may be an infiltrating one. Cystic softening is not infrequent (Fig. 349).

Microscopically, the appearance varies considerably, and the growth may be composed of round cells, spindle cells, or cells of various shapes. Not rarely a certain number of striped muscle-fibers are found, and to such growths the term *rhabdomyosarcoma* has been applied. In other cases there may be embedded in the sarcomatous tissue glandular acini composed of cylindrical or irregular epithelium, and to such the name *adenosarcoma* (Wilm's tumor) is given (Fig. 350). Occasionally, myxomatous tissue, smooth muscle-fibers, or even islets of cartilage are found. The multiform character of sarcoma of the kidney suggests an embryonal origin, and it is not unlikely that inclusions of the primitive Wolffian body are the starting-point of the disease.

The sarcomata of adult life are usually round or spindle celled, but angiosarcomata have been seen.

Adenoma of the kidney is rare. It originates in the convoluted tubules, and presents itself in the form of more or less nodular masses.



Fig. 35C.—Adenosarcoma or Wilm's tumor of kidney.

Microscopically, the appearance is that of a tubular adenoma. Proliferative changes occasionally affect the uriniferous tubules in interstitial nephritis, and give rise to small areas of adenomatous appearance. In such cases, however, the appearances are not those of a tumor in the strict sense.

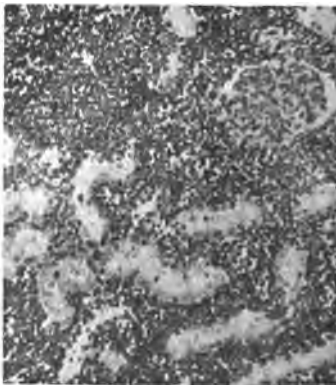


Fig. 351.—Lymphoid infiltrations between the renal tubules; from a case of leukemia.

Papilliferous cystic adenoma is sometimes observed. It occasions tumors of small or large size with fibrous capsules and cystic excavations in which the lining epithelium is elevated in a papillomatous manner.

Carcinoma is a rare primary tumor of the kidney, and occurs in persons of advanced years. The growth begins in the cortical substance or in the medulla, and presents itself as a soft white or, in case of hemorrhage into it, red tumor.

Microscopically, it is found to be a glandular carcinoma presenting acini composed of epithelial cells of various shapes. Metastasis is rare.

Secondary Tumors.—Among the secondary tumors of the kidney are both sarcoma and carcinoma.

In the same group may be included the *lymphomatous infiltrations* of leukemia (Fig. 351). In this disease the kidney is often enlarged, and on section is found to be uniformly white or mottled in color, the light-colored areas representing masses of lymphoid cells. Most of these



Fig. 352.—Large retention cyst of kidney (from a specimen in the Museum of the Philadelphia Hospital).

have doubtless been deposited from the circulation, but there is also evidence of local multiplication.

Cysts of the kidney are of various forms. In the course of chronic nephritis, especially the interstitial form, cystic dilatations of the convoluted tubules and Malpighian bodies are observed. These appear as small or large rounded bodies lying immediately beneath the capsule, and on section are found to contain serous liquid, or colloid material, the result of degeneration of the epithelial lining of the cyst. Some-

times very large cysts of this character are met with in cases of nephritis or even in otherwise healthy kidneys (Fig. 352). Cysts observed in kidneys which show no other disease are probably due to undiscovered obstructions of the uriniferous tubules.

Congenital cystic kidneys are of striking appearance. Usually both kidneys are affected, and are transformed into masses composed of innumerable cysts varying in size from microscopical points to cavities as large as a walnut (Figs. 353, 354). On section, the cysts are found



Fig. 353.—Congenital cystic kidney (Specimen 2816, Museum New York Hospital).

to be filled with clear urinous liquid or with colloid material, and between them is a stroma of more or less firm fibrous tissue. The pelvis of the kidney is usually preserved. These cysts are formed by dilatation of the uriniferous tubules and Malpighian bodies, probably as the result of some fetal disease which causes obstruction of the tubules at their outlet at the apex of the pyramids, or in consequence of faulty union between the upper and the lower segments of the uriniferous

tubules in the development of the organ. Similar cystic degeneration, with enlargement of one or both kidneys, may occur in later life. Such cystic kidneys have their origin in congenital conditions, even though the



Fig. 354.—Congenital cystic kidney.

enlargement does not take place until middle or more advanced age. Finally, cystic adenoma may again be mentioned.

PARASITES

Bacteria occur in the kidney in various affections: thus pneumococci, typhoid bacilli, and the bacilli of glanders and anthrax have been repeatedly demonstrated. In pyelonephritis the *Bacillus coli communis* is probably the usual active etiological agent. Streptococci occur in the nephritis of septic conditions and in primary infectious nephritis of cryptogenic origin. Bacteria are occasionally found in the uriniferous tubules without gross lesions of the kidney, and are probably excreted with the urine.

Animal parasites are occasionally observed, such as echinococcus cysts, filariæ, the eggs of *Fasciola hepatica*, amebæ, and infusoria.

Round-worms and the oxyuris sometimes migrate into the bladder or enter through fistulæ.

The echinococcus cyst occurs in the form of hydatids, which may perforate into the pelvis of the kidney and discharge with the urine, or become inspissated and calcify. The *Cysticercus cellulosæ* and *Linguatula rhinaria* are extremely rare. The *Filaria bancrofti* occurs in the lymphatic spaces and in the blood-vessels of the kidney in cases of filariasis with chyluria. The kidneys in these cases show a waxy appearance on section, especially toward the apices of the pyramids, and the surface of the kidney may be abnormally lobulated. Microscopically, the lymphatic spaces about the uriniferous tubules are greatly distended.

The *Schistosoma hematobium* occasionally produces pyelitis and pyelonephritis, with enlargement of the pelvis of the kidney.

THE PELVIS OF THE KIDNEY AND URETER

CONGENITAL AND ACQUIRED MALFORMATIONS

Occasionally the pelvis or ureters, or both, may be absent or imperfectly developed. Complete obliteration of the ureter may be observed. More frequently there are two pelves or ureters, and when this is the case the malformation is, as a rule, bilateral.



Fig. 355.—Dilatation of the ureter due to calculous obstruction.

Obstructions of the ureter may be due to twists, to congenital atresia, or to other diseases of the ureter, particularly at its entrance into the bladder. It may be brought about by the lodgment of renal calculi, by tumors of the ureter, or by pressure upon it from without. The outflow of the urine may be obstructed by diseases of the bladder, and particularly by stricture of the ureter.

Dilatation of the ureter results from the conditions just named, and may reach considerable dimensions (Fig. 355). When the obstruction is continued the dilatation may affect the pelvis of the kidney as well, and eventually the latter may be enormously enlarged. The pyramids become flattened, and the renal substance may undergo progressive atrophy, so that the kidney is converted into a sac-like formation filled with clear liquid, partly urine secreted in the earlier stages and partly transudate formed after the compression has stopped the renal function. To this condition the term *hydronephrosis* is applied.

CALCULUS

Calculi are of frequent occurrence in the pelvis of the kidney, and are formed by the precipitation of various normal or abnormal constituents of the urine. There may be merely small gritty particles lying in the calices or in the pelvis, to which the term *renal sand*, or *gravel*, is given; or there may be large stones, almost filling the pelvis and calices, and forming more or less accurate moulds of these. The most frequent forms are those composed of uric acid and oxalate of lime, but phosphate and carbonate of calcium and triple phosphate calculi are occasionally found. Stones composed of cystin and xanthin are rare. Uric-acid calculi are composed of the acid itself or of urates, and present themselves as yellowish, brownish or red, smooth, or somewhat irregular formations. Those composed of oxalate of lime are irregular in shape and of brownish or red color.

The results of renal calculi may be trivial or serious. Small particles of renal sand are frequently passed without serious disturbance. Large calculi tend to set up inflammation of the pelvis of the kidney, and may obstruct the outflow of the urine, causing hydronephrosis (Fig. 356). In some cases cancer seems dependent upon the continued irritation of a retained calculus. Those in the pelvis or ureter may pass down to the bladder, with the clinical picture of renal colic, or they may be caught in the ureter along its course or at the bladder opening. If caught, ureteritis or hydro-ureter may arise. In its passage the stone may so damage the ureter as to cause stricture.



Fig. 356.—Calculus in upper part of ureter and pelvis of kidney.

INFLAMMATION

Inflammation of the pelvis, or pyelitis, may result from the irritation of poisons ingested, such as cantharides, turpentine, and the like, or it may occur in the course of infectious diseases of various kinds. More frequently it results from the irritation of a calculus, or from ascending inflammation consequent upon cystitis and ureteritis. The infection passes upward by continuity or along the ureteral lymphatics; a pericystitis and periureteritis may also lead to a pyelitis. The mucous membrane becomes reddened and swollen, and not rarely is marked with hemorrhagic ecchymoses. The surface is covered with desquamated epithelium and pus-cells. The inflammation may extend

to the substance of the kidney (*pyelonephritis*). Considerable purulent exudate may take place, particularly when there is a calculus partially obstructing the ureter. When there is complete obstruction the pelvis may become dilated with pus, and the calices or the entire kidney may be converted into a large pus-sac (*pyonephrosis*). Deposits of triple phosphate may occur in pyelitis, and may occasion incrustations upon the mucous surface.

Inflammation of the ureter, or ureteritis, may occur under the same conditions as pyelitis. The mucous membrane of the ureter becomes swollen and reddened, as in catarrhal inflammations elsewhere, and there may be erosions or superficial ulcerations. The other coats are thickened by inflammatory infiltration and, in chronic cases, by fibrous-tissue overgrowth.

INFECTIOUS DISEASES

Tuberculosis of the pelvis of the kidney may occur as a miliary tuberculosis, or in the form of caseous nodules or masses. The latter may be primary and hematogenous in origin, or may result from ascending infection (Fig. 357). It seems from later observations that the



Fig. 357.—Tuberculous pyelonephritis (modified from Bollinger).

tubercle bacillus passes up the unobstructed ureter by means of the lymphatics in the wall of this tube. When obstructed the passage of germs occurs by extension or aided by the changes in pressure between

the bladder and the pelvis because of the impeded downflow of urine through the ureter.

In such instances the mucosa becomes more or less extensively infiltrated, and later caseous and ulcerated. The process extends to the calices, and subsequently to the pyramids and other parts of the substance of the kidneys. The pelvis may contain considerable quantities of caseous or puriform matter, and the kidney substance may be extensively involved. The urine contains pus-corpuscles and often



Fig. 358.—Tuberculous nodule in the wall of the ureter, with beginning hydronephrosis (from a specimen in the Museum of the Philadelphia Hospital).

tubercle bacilli in great numbers. Tuberculosis of the ureters leads to nodular or diffuse thickening, and commonly to more or less obstruction (Fig. 358).

TUMORS

Primary cancer is extremely rare. Secondary cancer may affect the pelvis in association with the kidney, or the ureters in association with the bladder. Small cystic formations are not uncommonly seen in the mucous membranes of the ureters, and may be due to inflammatory obstruction of the crypts, to proliferation and softening of the lymphoid follicles, or to parasitic invasion (*psorospermia*).

PARASITES

Round-worms have occasionally been found in the ureters. The eggs of *Schistosoma hæmatobium* are frequently deposited in the mucous membrane, and occasion inflammation and papillomatous excrescences.

THE URINARY BLADDER

MALFORMATIONS

Congenital malformations of the bladder are comparatively common. Among the more important is *exstrophy*. The anterior wall of the abdomen and of the bladder being wanting, the mucous membrane, with the openings of the ureters, is exposed to view. Not uncommonly this condition is associated with epispadias, or division of the clitoris. Sometimes the small intestine discharges through the exstrophic bladder, the large intestine being contracted or completely absent.

Occasionally the urachus remains patulous in consequence of atresia of the neck of the bladder or urethra, and the urine is discharged from the umbilical end. In other cases the urachus is closed at either end and the intervening portion is dilated, with the formation of a cyst. Again, there may be only partial obliteration of the urachus, the remaining portion in connection with the bladder being patulous and greatly dilated, forming a congenital adventitious sac. In a case known by one of us this constituted a cavity of considerable size, and when filled distended the abdomen as far as the umbilicus. Congenital diverticula may occur in the anterior wall, and less commonly at the sides of the bladder. Complete absence of the bladder, division into lateral portions by a septum (*vesica bipartitis*), and other congenital defects are rare.

Acquired Malformations.—*Dilatation of the bladder* may result from congenital or acquired stenosis of its neck, or of the urethra; or from paralysis of its walls, in consequence of disease of the spinal cord or nerves. The organ may be greatly increased in size, often reaching the umbilicus. When the dilatation is acute the walls are greatly thinned, but when it has been gradually developed compensatory hypertrophy of the muscularis and of the submucous fibrous tissues leads to thickening of the walls. In these cases the mucous surface presents a ribbed appearance, fibrous-tissue bands standing out prominently and the mucosa being pouched between the bands. Diverticula of considerable size may form in this way, and the walls of the bladder sometimes present a considerable number of pouches.

CHANGES OF POSITION

The position of the bladder, or of portions of it, is sometimes abnormal. Thus, it may enter into a hernia, or a part of the wall of the bladder may prolapse with the wall of the vagina, forming vaginal cystocele. The latter is due to the traction of the prolapsing uterus or to repeated overdistention of the bladder, with weakness of the anterior vaginal wall. Complete inversion of the bladder through the urethra has been observed in women.

RUPTURE

Rupture of the bladder may be due to traumatism, and particularly to perforation by fractured pelvic bones. Rupture from overdistention is rare. Occasionally it may result from abdominal compression when the bladder is distended with urine, and ulcerative processes beginning in the mucous membrane may perforate the wall, or phlegmonous inflammations or degenerating new growths surrounding the bladder may lead to perforation. In women perforations are frequently established between the bladder and vagina in consequence of pressure of the fetal head or of forceps, and vesicovaginal fistula results. Perforation into the peritoneal cavity is usually followed by fatal acute peritonitis. Rupture into the tissues below the peritoneal reflections gives rise to widespread infiltration of urine and phlegmonous or gangrenous inflammation.

CIRCULATORY DISTURBANCES

Active hyperemia may result from irritant poisons, such as cantharides, or may occur in persons suffering from paraplegia, in consequence of disturbances of innervation or, possibly, by high acidity of the urine.

Passive hyperemia occurs when there is pressure upon the inferior vena cava or thrombosis of that vein. The mucous membrane becomes dark red and is often marked with punctate hemorrhages. Considerable varicosity of the veins at the neck of the organ may occur, and may give rise to edema, to copious hemorrhages, or to obstruction and retention of the urine.

Hemorrhages in the mucous membrane occur in severe congestion or inflammation, and in various hemorrhagic diseases. Large hemorrhages into the cavity itself may result from traumatism from without or from calculi. The varicosities before mentioned may occasion considerable hemorrhage, as may also papillomatous or other new growths. Large quantities of blood with little admixture of urine may lead to the formation of dense clots within the organ, but when the quantity is small the blood is mingled with the urine.

INFLAMMATION

Inflammation of the bladder, or cystitis, varies in extent, duration, and character. Acute cystitis may result from irritant poisons excreted with the urine from infectious processes extending from the renal pelvis or ureter, and frequently attends acute infectious diseases. In these cases, however, the disease is generally mild. More intense forms occur from extension of inflammation to the bladder in cases of urethritis, or when septic material is introduced in catheterization. Retention and decomposition of the urine from strictures or prostatic hypertrophy are frequent causes of chronic cystitis. The most common

organisms in cystitis are micrococci and colon bacilli. These organisms may ascend the urethra, descend from the ureter, or extend through the neck of the bladder from its related glands. The urine is usually alkaline except in cases of colon bacillus infection, when acidity is the rule.

Cystitis may present itself as a mucopurulent catarrh, acute or chronic in course; as phlegmonous inflammation; or as a pseudomembranous process.

Mucopurulent cystitis in the acute stages causes swelling of the mucous membrane, with injection of blood-vessels and sometimes punctate hemorrhages. The surface, especially at the base, is covered with mucopurulent exudate of a tenacious character, in which pus-cells and desquamated epithelium are abundant. The urine tends to undergo ammoniacal fermentation.

In chronic cases thickening of the submucosa and hypertrophy of the muscularis cause great thickening of the organ, and the surface within is usually ribbed from the prominence of the fibrous-tissue

bands and the pouching of the mucous membrane between the bands (Fig. 359). Erosion and ulceration may occur upon the surface, and occasionally perforation of the walls takes place. Incrustations of triple phosphate and of other common salts frequently cover the surface.

Phlegmonous cystitis results from intense infections; infrequently occurs in the flabby bladder of paraplegia when there is retention of urine. The submucous tissue is considerably swollen and infiltrated, and complete perforation of the walls and paracystitis or phlegmonous inflammation of the tissues surrounding the bladder may ensue.



Fig. 359.—Dilated ribbed bladder.

Pseudomembranous cystitis occurs in certain severe infectious diseases, and may present itself in the form of a typical pseudomembrane, or as a combination of phlegmonous and pseudomembranous inflammation. Occasionally, pseudomembranes are formed without any inflammatory process in nervous individuals, and in the course of or after pneumonia a cast of the entire bladder of this nature has been seen by one of the authors.

Chronic cystitis may follow an acute attack or be primarily a progressive process. There is either a hypertrophy of the mucosa, with irregular papillomatoid outgrowth, or a thinning of the layer by atrophy. The secretion varies, but it is usually mucopurulent and covers closely the variegated or uniformly slate-colored mucosa. This color is due to altered blood-pigment. The muscular coat undergoes fibrous thickening and the contractility is impaired.

INFECTIOUS DISEASES

Tuberculosis of the bladder is usually secondary to tuberculosis of the kidney, or to that of the prostate, seminal vesicles, or epididymis. Tuberculous ulcers independent of tuberculosis elsewhere in the urogenital tract may occur in phthisis or intestinal tuberculosis, but such cases are rare. The lesions observed in tuberculosis of the bladder are ulcerations, beginning in mucosa and submucosa, miliary tubercles for the most part occupying the base of the organ and surrounding the orifices of the ureters, and there may be distinct or clustered tubercles.

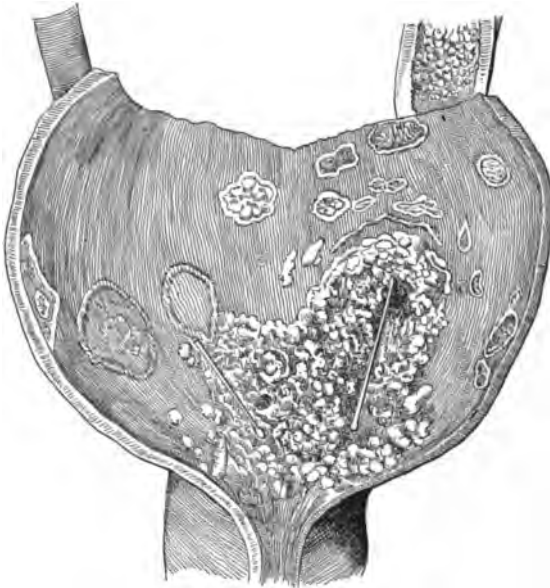


Fig. 360.—Tuberculosis of the bladder (Orth).

Numerous small ulcers or a single large ulcerated surface may be observed (Fig. 360). Deposits of triple phosphate frequently form incrustations on the surface.

Syphilitic ulcers and **gummata** have been observed in the bladder, but are extremely rare.

CALCULI AND FOREIGN BODIES

The bladder is the commonest seat of urinary calculi. They may occur in the form of fine particles or gravel, or as stones of considerable size. Usually there is but one; sometimes a considerable number may be present. The shape and general appearance depend upon the composition of the stone.

The formation of calculi is due to precipitation from the urine of its various earthy or other constituents as the result of stagnation

and fermentative change. Foreign bodies often form the nuclei of stones, and thus a calculus in the bladder may form around broken portions of catheters, hairpins, or other foreign bodies inserted into the urethra. Similarly, parasites may be the nucleus, but in ordinary cases of stone mucus or degenerated epithelial cells constitute the focus about which the deposit occurs. Catarrhal conditions of the bladder, especially when combined with stagnation of the urine as the result of hypertrophy of the prostate, urethral stricture, and the like, are the most common antecedent causes. The nucleus being present it attracts mucus and other organic matter; this forms a matrix in which salts are deposited, probably in some chemical combination with the organic matter since they are not found in their ordinary crystalline forms.

Calculi in the bladder may be composed of uric acid or urates, of oxalate of lime, of various phosphates, of carbonate of lime, or of certain organic compounds.

Uric acid and urate calculi are less common in the bladder than in the kidney. They result from surcharge of the urine with uric acid in lithemic or gouty individuals, and from acid decomposition rendering the uric acid and urates insoluble. Uric acid calculi are yellowish or red in color, rounded, slightly granular or smooth upon the surface, and, as a rule, quite hard. The calculi composed of urates are usually more irregular and softer, and are generally lighter in color. Frequently phosphates are combined with them. These stones may be started in the kidney pelvis, especially in the young, and there assume somewhat the shape of the kidney hilus.

Phosphatic calculi may be of several kinds: they may be composed of phosphate of lime, triple phosphate, or mixed phosphates. They form the most frequent variety of calculi and concretions in the bladder, and are generally due to alkaline decomposition causing a deposit of the simple phosphate of lime or of the combination of phosphate of magnesium with ammonium phosphate, known as triple phosphate. These deposits may occur in the form of incrustations upon the surface of the bladder in various diseases, or in the form of irregular, soft, and more or less white calculi.

Oxalate of lime occasions rounded, hard calculi, of brownish color and of irregular, granular surface, from which they derive the name *mulberry calculi*. They occur in conditions similar to those causing uric-acid stones.

Calculi composed of carbonate of calcium, sulphate of calcium, cystin, xanthin, and indigo are extremely rare.

Results of Urinary Calculi.—While cystitis and retention of urine favor calculus formation, the latter is prone to occasion increased irritation and inflammation, and may cause serious obstruction to the outflow of urine, and thus retention in the bladder. Ulceration may take place, and perforation of the bladder-walls may ensue. Hypertrophy of the walls occurs when the stone only partially obstructs the outflow, and under the same conditions the ureters may become distended and hydronephrosis may occur. Not rarely the stone lies in a pouched dila-

tation of the wall of the bladder, either from having been formed in that situation in consequence of stagnation of the urine, or from having caused a dilatation by weakening the walls at a certain point. Complete encapsulation of the stone has been observed in such cases.

Various objects are found as foreign bodies in the bladder. They include most commonly the products of inflammation higher up, such as casts or tissue cells, but bodies are sometimes introduced through the urethra. Hairpins, tooth-brushes, matches, etc., have been found. Occasionally parasites are found in the bladder (*filarix* and *distoma*).

TUMORS

Polypoid outgrowths from the mucosa may be observed in chronic cystitis.

Papillomata occur either as the result of chronic irritation or as apparently causeless tumors. The papilloma presents itself as a somewhat cauliflower-like elevation affecting the base, and sometimes considerable portions of the mucosa, and has a whitish or grayish color.



Fig. 361.—Tuft of papilloma of the bladder.

It is usually vascular and, therefore, frequently occasions hemorrhages.

Microscopically, it is composed of a delicate connective-tissue stroma containing large, thin-walled blood-vessels, and covered with cylindrical epithelium (Fig. 361). Occasionally papillomata become transformed into malignant epitheliomatous growths.

Carcinoma is a rare form of primary tumor. It occurs as a somewhat papillomatous thickening of the mucosa, or as a more considerable infiltration of the wall of the bladder (Fig. 362). Microscopically, it is composed of large polymorphous epithelial cells infiltrating the walls more or less deeply and irregularly, or arranged in acini or alveolar formations.

Secondary carcinoma of the bladder may result from extension of prostatic or uterine cancer. Very rarely the bladder is involved by metastasis.

Fibroma, fibro-adenoma, myoma, and myxoma are occasionally observed, and *cysts* may be formed by closure of pouched diverticuli or



Fig. 362.—A, Epitheliomatous tumor; B, wart-like growths; C, villous growths (Clado).

by distention of the patulous urachus. Cysts of obscure origin are sometimes met with; dermoid cysts are rare. *Sarcoma* is very rare.

ABNORMAL CONDITIONS OF THE URINE

Quantity.—The normal quantity in the adult is from 1500 to 2000 c.c. Conditions which check the perspiration or action of the bowels increase the amount of urine; excessive sweating and diarrhea have the reverse effect. In the latter case the excretion may be almost suppressed (*anuria*). The same may occur in acute nephritis or chronic nephritis with uremia, in extreme anemia, and in acute or chronic

obstructive conditions in the gastro-intestinal tract interfering with absorption of water. Occasionally, anuria is reflex, resulting from obstruction of the urinary passages by calculi. The quantity of urine is increased (*polyuria*) in cases of excessive consumption of water, and habitually in diabetes mellitus and insipidus and in chronic interstitial nephritis. The amount of urine is also influenced by the blood-pressure; increased flow follows high arterial pressure, while decrease follows low arterial and high venous pressures.

Specific Gravity.—Normally the specific gravity is 1015 to 1020. It becomes increased when the amount of urine is decreased, and *vice versa*. The specific gravity is especially high in diabetes mellitus, despite the polyuria, sometimes reaching 1040 or 1050. It is low in most forms of chronic nephritis, in diabetes insipidus or simple polyuria, and in anemia and hysteria, or other nervous diseases.

Color.—The normal amber color is due to the presence of various pigments, especially urobilin and uro-erythrin. These are derivatives of hemoglobin or bilirubin.

In pathological conditions other pigments, such as hematoporphyrin, pathological urobilin, melanin, etc., are met with. Indican is present in the urine in the form of a chromogen, which may sometimes become oxidized, with the formation of dark-colored pigment-animal-indigo. Certain drugs eliminated with the urine cause discolorations. Bilirubin occurs in jaundice and other conditions, and blood or hemoglobin may cause discoloration.

Reaction.—The normal reaction is acid, but frequently after meals it becomes neutral or even alkaline. The ingestion of certain foods rich in alkalis or acids, which become converted into alkaline carbonates (citrates, acetates, etc.), may occasion an alkaline reaction, while other acids lead to the opposite result. Decomposition of the urine usually causes an intense alkaline reaction by conversion of the urea into ammonia. Occasionally the reaction of the urine is amphoteric, both red and blue litmus-paper being acted upon.

Glucosuria is a term applied to the presence of glucose or grape-sugar in the urine. The condition is discussed in the chapter on Disorders of Metabolism.

Levulosuria, the presence of fruit-sugar; **lactosuria**, that of milk-sugar; and **dextrinuria**, that of dextrin in the urine, have been discovered.

Pentosuria is a condition in which pentoses, sugars containing five atoms of carbon in each molecule, appear in the urine. The condition is important mainly because pentoses react to certain reduction tests (Fehling's, Trommer's) like glucose. They do not polarize light nor ferment as does glucose. Pentosuria is a metabolic disorder of uncertain character sometimes occurring independently, sometimes in association with diabetes. It is not the result of disordered metabolism of starches, and the source of the pentoses is uncertain, though it is not improbable that they are derived from nucleoproteins of various organs; being therefore endogenous, since they may be excreted in quantity greater than

present in the food, and such patients seem to have a tolerance to the ingestion of pentose.

Alkaptonuria is a metabolic disturbance in which the urine turns black after excretion. The addition of alkalis to the fresh urine causes immediate change to a dark or black appearance. The chemical substances concerned in this phenomenon are homogentisic acid and sometimes uroleucinic acid, aromatic acids derived from protein metabolism. These substances are in part derivatives of albumins of the food, but always also in part the products of metabolic destruction of tissue proteins. Their appearance in the urine has been ascribed to the lack of ferments which normally destroy these substances. It has also been held that homogentisic acid is formed in the intestines by bacterial processes involving decomposition of tyrosin. Clinically, alkaptonuria has been found associated with diabetes, tuberculosis, and pyonephrosis. In a number of cases of alkaptonuria there has been found the peculiar black pigmentation of cartilages called by Virchow *ochronosis*. This at times affects superficial cartilages like those of the ear, where it causes visible discoloration. Besides alkaptonuria, chronic phenol-poisoning may also occasion ochronosis.

Choluria is the name indicating the presence of biliary pigments and acids in the urine. It is most frequently observed in cases of jaundice due to hepatic disease, but may also occur in so-called hemato-genous jaundice, the formation of the pigment in some of the latter cases probably taking place in the kidneys themselves. The urine presents a dark color, varying from brownish to greenish. Oxidizing substances, such as fuming nitric acid, produce a play of colors.

Microscopically, the cellular constituents of the urine are found stained, and granular concretions of bilirubin or rhombic crystals may be observed. Hyaline casts, more or less deeply stained by the pigment, are frequently seen.

Urobilinuria.—Urobilin occurs in the normal urine mainly as a chromogen, or is converted into urobilin on the addition of acid. Sometimes urobilin is present in large quantities in the fresh urine. This has been particularly observed in fevers, in jaundice, and in certain anemic diseases, especially in pernicious anemia. Its presence in large quantities is due to damage to the liver parenchyma.

Indicanuria.—Indigo-blue occurs in the urine as a chromogen which gives rise to the formation of indigo on decomposition. This indican, or indoxyl sulphate, is a product of indol derived from the intestine, and an excess of indican in the urine is significant of intestinal decomposition.

Other forms of the ether-sulphuric-acid series occur in the urine, but are less significant.

Acetonuria occurs to a slight extent in health, but more particularly in conditions of inanition, in gastro-intestinal disturbances, and in fever. It is especially significant in diabetes mellitus, and may become very pronounced toward the latter end of this affection.

Diaceturia, or the condition in which diacetic acid appears in the

urine, is also met with in fevers and inanition, but particularly in diabetes.

Lipaciduria refers to the presence of fatty acids in the urine, but has no special significance.

Hydrothionuria refers to the presence of sulphuretted hydrogen in the urine. This is noted occasionally in auto-intoxications or as the result of fermentative changes in the urine. The urine may have a foamy appearance, to which the term *pneumaturia* is sometimes applied. Other gases may be present, but only in small proportion and rarely.

Melanuria is a term applied to the dark discoloration of the urine occasionally seen in persons suffering from pigmented tumors. It also occurs in phthisis and other wasting diseases. As a rule, the urine becomes darker after addition of oxidizing substances, but it may be quite dark when passed. It contains iron and sulphur.

Albuminuria.—Minute traces of serum-albumin probably occur in the normal urine. The term "albuminuria," however, is applied to cases in which albumin is readily detected. It may be accidental—that is, dependent upon the admixture of albuminous substances from the mucous membrane lining the urinary passages—or essentially renal in character. In the former instances the presence of abundant blood- or pus-cells indicates the nature of the case. True renal albuminuria consists of the excretion with the urine of serum-albumin and serum-globulin, the former being considerably more abundant than the latter. Pure serumuria is extremely rare, and pure globulinuria perhaps even more so.

Albuminuria is more frequently the product of actual renal disease or nephritis, and is then due to the disease of the epithelium of the glomeruli and tubules. A certain amount of albumin occurs in degenerative or congested conditions of the kidneys; in various general diseases affecting the blood without manifest disease of the kidney, such as anemias, diabetes, toxemias, and the like; in certain nervous affections probably influencing the circulation; and in disorders of the digestive tract.

At times albuminuria is periodic or cyclic, this periodicity depending upon general conditions, such as diet, exposure, and exercise, which, in turn, affect the blood or renal circulation. Considerable amounts of albumin in the urine are never physiological. Large proportions of globulin occur in amyloid disease of the kidneys.

Albumosuria.—Various albuminous substances derived from serum-albumin or serum-globulin, and not coagulable by heat, occur in the urine. These are hydration products designated albumoses or propepton. True pepton has never been found in the urine. Albumosuria occurs in cases in which pus-cells or large exudates are undergoing absorption, as in septic processes, pneumonia, and the like (*pyogenic albumosuria*). In another group of cases intestinal malassimilation or decomposition comes into play (*enterogenic albumosuria*). In the third group diseases of the blood, such as leukemia and various intoxications,

are active (*hematogenic albumosuria*). A fourth, or puerperal, form occurs after labor. In the "albumosuria" of Bence-Jones, which accompanies myelomata, the abnormal substance is probably not an albumose, but a simple albumin.

Nucleo-albuminuria.—Nucleo-albumin, formerly supposed to be mucin, is derived from the protoplasm of the surface epithelium of the urinary tract, and occurs in the urine in small quantity in nearly all persons, and in large quantity when there is irritation of the lining mucosa, particularly in pyelitis and cystitis.

Cystinuria is a disorder of metabolism in which cystin, a nitrogenous sulphur compound, appears in the urine. Cystin is a normal intermediary product of metabolism which is further oxidized and, therefore, does not appear in the urine. In cystinuria there is a retardation or absence of this oxidation. In some cases diamin, putrescin, and cadaverin have been found associated with cystin. This appears to represent an advanced grade of the same metabolic disturbance. Cystinuria may occasion no symptoms; but sometimes cystin calculi are formed in the kidney or bladder.

Fibrinuria occurs in conditions in which lymph or blood gains access to the urinary passages. Fibrinous casts or shreds may be passed, or small flocculent particles are observed. Fibrinuria is usually associated with hematuria or chyluria.

Hematuria is a term applied to the presence of blood in the urine. This may be accidental from admixture of menstrual blood and the like, or may be a pathological condition, in which the blood originates from the kidneys, ureters, bladder, urethra, or other parts of the urinary system. Renal hematuria may result from intense congestion or from hemorrhagic nephritis. Traumatism, either from without or from calculi in the pelvis, is a frequent cause. Tumors and specific inflammatory processes are occasional causes. Sometimes hematuria is due to intense anemia, hemorrhagic diseases, or severe intoxications. Hematuria which is due to admixture of blood with the urine below the kidney results from traumatism, injury by calculi or catheterization, from vascular tumors, and occasionally from inflammatory or other disease processes.

Renal hematuria is distinguished from that originating in the bladder by the intimate admixture of urine and blood, and by the associated evidences of renal disease—renal epithelium, tube-casts, etc. Fragmentation of the red corpuscles is said to indicate renal hematuria. In hematuria originating in the bladder larger clots may pass, in association with bladder epithelium and mucin (nucleo-albumin). In cases of sudden renal hemorrhage large clots, sometimes forming casts of the pelvis, may be formed and discharged.

Hemoglobinuria indicates the presence of free hemoglobin or of methemoglobin in the urine, without the presence of blood-corpuscles. Hemoglobinuria results from causes which lead to disorganization of blood and elimination of the coloring-matter through the kidneys. It is met with in various infectious diseases, such as malaria, and in in-

toxications, as in poisoning with potassium chlorate, carbolic acid, arsenic and other drugs, or with toadstools. It occasionally results from snakebite or poisoning by other venomous animals.

Paroxysmal hemoglobinuria is a form of intermittent disease especially frequent in subtropical countries. The attacks sometimes seem to be determined by exposure to cold and other external influences, while the predisposition may be dependent upon syphilis or other general disorders. The urine presents a dark-red or brownish color, and when tested with the spectroscope shows the bands indicative of hemoglobin or methemoglobin.

Microscopically, the hemoglobin may present itself in the form of granules or cast-like formations, or sometimes as crystals. Blood-corpuscles are absent or, at most, present in extremely small numbers.

Lipuria.—A small amount of fat may appear in the urine in cases of advanced diffuse nephritis with fatty degeneration, and in certain cases of pyelitis. In other cases lipuria results from disorders in which there is excess of fat in the blood (lipemia). This occurs in cases of excessive consumption of oil or fatty food and in cases of intoxication, notably by arsenic. It is sometimes present in diabetes, phthisis, chronic alcoholism, and obesity, and fractures injuring the marrow or serious traumatism of the subcutaneous fatty tissues may cause fat embolism and lipuria.

The appearance of the urine varies with the amount of fat, but, as a rule, there is a solid scum upon the surface, and there may be large oil-drops. Occasionally the urine is quite milky when recently passed. Microscopically, oil-drops are more or less abundant, and fat-crystals may be discovered.

Chyluria is the name applied to a milky condition of the urine which probably results from admixture of lymph or chyle. The urine is light colored, and more or less milky in appearance. Often there is a reddish discoloration from associated hematuria (*hematochyluria*). The urine contains albumin and sometimes albumoses.

Microscopically, numerous oil-drops of varying size and, usually, blood-corpuscles are detected. The most frequent cause is the obstruction of the lymphatic channels and their subsequent rupture in the kidney or bladder in consequence of the lodgment of the *Filaria sanguinis hominis*. In these cases the embryos of the filariæ are usually detected in the urine. Sometimes a chyluria is non-parasitic, but the causes are obscure.

Bacteriuria.—Normally, the urine contains no bacteria. In cases of cystitis or other inflammatory diseases, however, and particularly when catheterization has been practised, bacteria of decomposition may be present, such as the *Micrococcus ureæ*, *Bacterium termo*, the *Bacillus proteus*, yeast fungi, and other forms. Not rarely the *Bacillus coli communis* is met with, particularly in ascending infections of the urinary tract. In cases of certain infectious diseases, such as typhoid fever, pneumonia, and erysipelas, the specific micro-organisms may be found in the urine, having escaped from the blood through the capillaries of

the glomeruli. Streptococci are also met with in primary and secondary infectious nephritis. Pseudodiphtheria bacilli are so common upon the genitalia and in the urethra that it is common to find them in voided urine. The tubercle bacillus may be discovered in cases of tuberculosis of the kidney, ureters, bladder, or other parts of the urinary tract (Fig. 363). It is frequently present in clusters, this constituting a marked point of distinction from the smegma bacillus, which is often found in urine, especially that of women, and is easily mistaken for the tubercle bacillus. Another point of distinction is the greater ease

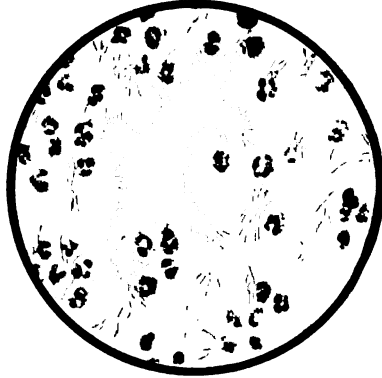


Fig. 363.—Tubercle bacilli in the urine; from a case of tuberculous cystitis (Jakob).

with which the smegma bacillus, stained with carbolfuchsin, may be decolorized by alcohol. Positive differentiation in doubtful cases is made by injection of the urine into guinea-pigs.

CHEMICAL CHANGES AND SEDIMENTS

The various inorganic and organic constituents of the urine may be present in excessive quantities, and may form deposits, or abnormal chemical substances may be detected.

Uric acid is deposited in the form of yellowish, brownish, or reddish crystals of whetstone shape, or as irregular angular formations superimposed or clustered together (Fig. 364). The color is due to uro-erythrin taken up from the urine. The crystals of uric acid may deposit from a highly acid urine, even though there be no excess.

Oxalate of lime occurs in the form of highly refracting octahedral corpuscles, their appearance being likened to that of an envelope (Fig. 365). Certain foods rich in oxalates may cause excessive excretion, and oxaluria occurs as an independent condition of obscure nature allied to gout and lithemia. Oxalates deposit from highly acid urine, even though no excess be present. This must be distinguished from oxaluria proper.

Phosphates.—Various forms of phosphates are found in crystalline form in urinary sediments. Basic phosphate of magnesium and neutral

phosphate of lime are found in urine becoming alkaline, while the phosphate of ammonium and magnesium, or triple phosphate, is met with when alkaline decomposition takes place. It presents itself in different forms, the most characteristic being the large coffin-lid crystals and certain star-shaped formations (Fig. 366). Triple phosphate is espe-



Fig. 364.—Various forms of uric acid crystals.



Fig. 365.—Various forms of crystals of oxalate of calcium.

cially abundant in cystitis with alkaline decomposition of the urine in the bladder.

Urates are deposited from acid urines as a whitish or reddish sediment of amorphous character. The reddish color sometimes observed is due to admixture of urinary pigment. In decomposing urine, of

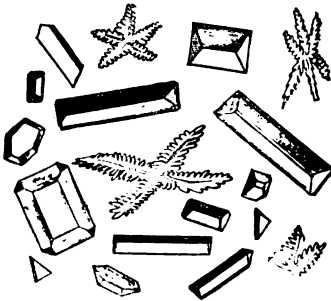


Fig. 366.—Crystals of triple phosphate (ammonium-magnesium phosphate).

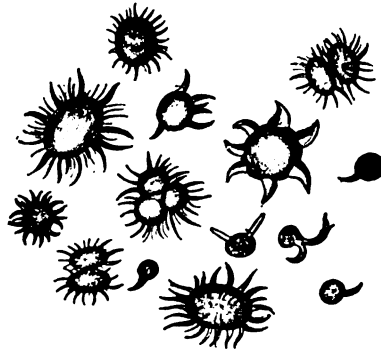


Fig. 367.—Urate of ammonium crystals.

somewhat alkaline reaction, urate of ammonium is deposited as hedgehog crystals or masses (Fig. 367).

Hippuric acid is rarely met with, excepting after the ingestion of benzoic acid or of certain fruits. It forms long, prismatic crystals, which occur in groups.

Carbonates and sulphates are rarely observed in urinary sediments.

Fat-crystals occur in the form of fine needles, or of aggregations arranged in a star-like manner and resembling tyrosin groups (Fig. 368). They are found in cases of chronic nephritis, pyelitis, and cystitis.

Tyrosin.—This substance usually occurs in the urine in solution, or rarely in the form of sheaves composed of fine needles arranged in star-like clusters (Fig. 368).

Leucin occurs as small spheres, often having a somewhat radiated structure within. These are most readily discovered when the urine has been partially evaporated.

Leucin and tyrosin are observed in acute yellow atrophy of the liver, in phosphorus-poisoning, and occasionally in severe infectious fevers.

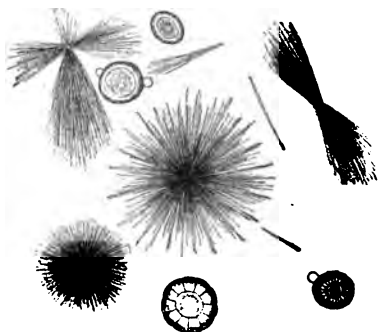


Fig. 368.—Leucin spheres and tyrosin needles.

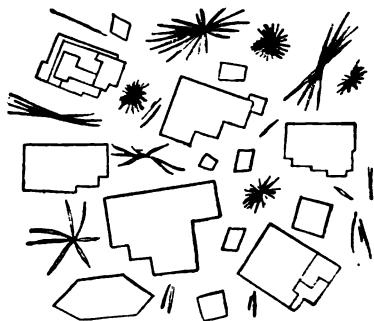


Fig. 369.—Cholesterin plates and fat-crystals (needles).

Cystin occurs in the form of hexagonal plates often superimposed. They are most frequently associated with cystin calculi in the kidney.

Xanthin is extremely rare, but may be associated with xanthin calculus.

Cholesterin appears in the form of flat, quadrilateral plates, with a re-entering angle at one of the corners (Fig. 369). They are met with in old cystitis or pyelitis, but are rare.

Indigo.—Amorphous particles or crystals of indigo may be found in urine containing great excess of indoxyl sulphate. They present a characteristic bluish color.

Bilirubin, hemoglobin, methemoglobin, and hematoidin are occasionally seen as brownish granular concretions or in the form of rhombical crystals. (See Chyluria, Hemoglobinuria.)

THE URETHRA

CONGENITAL ABNORMALITIES

Absence of the urethra is sometimes met with in association with other defects of development. Partial deficiencies and abnormal structure of the urethra are more frequent. Thus in the female it may be reduced in length and open in the anterior wall of the vagina, and in the

male may terminate at the base of the scrotum. Obliteration of part of the urethra (atresia) may occur in cases of defective development of the *corpus spongiosum*; more commonly there is obliteration of the meatus. Other abnormal conditions will be considered in connection with defective development of the penis.

INFLAMMATIONS

Inflammation of the urethra, or urethritis, is most frequently due to a specific micro-organism—the gonococcus of Neisser. Some cases, however, are non-specific, resulting from irritation by chemical or mechanical agents with associated infection (staphylococci, streptococci, or other organisms). Some of these cases are caused by direct traumatism, as by blows, injuries caused by catheterization, and the like; in other cases foreign bodies, as calculi, become lodged in the urethra and occasion inflammation or injure the urethra in passing. Urethritis, like inflammations of other mucous membranes, may occur in various infectious diseases, such as typhoid fever, scarlet fever, small-pox, etc. In the female, inflammations of the vagina and vulva frequently extend to the urethra. A form of pseudomembranous urethritis of obscure origin has been observed in a few cases.

Specific urethritis, or *gonorrhea*, is always due to direct infection with the gonococcus (for description of the organism, see Part I). Certain conditions of the urethra favor infection; thus an adherent prepuce, by causing greater retention of the infective matters, increases the liability, and probably congested and irritated states of the urethral mucosa heighten the susceptibility. The vulnerability of different individuals probably varies; and doubtless the micro-organism has greater virulence in some instances than in others.

Pathological Anatomy.—Urethritis usually first affects the mucosa at or near the meatus, but tends to spread rapidly to the posterior parts. The mucosa is at first intensely congested, red, and swollen. Soon a purulent exudate, of yellowish or greenish color, makes its appearance. The small crypts or lacunæ swell and become distended with purulent exudate.

Microscopically, urethritis presents the features of an intense purulent catarrh. Within a few days of the onset the superficial epithelium becomes loosened and begins to desquamate; and at the same time polymorphonuclear leukocytes make their way to the surface between the epithelial cells. The pus-cells and epithelium of the surface exudate contain gonococci in abundance, and the organisms are discovered in the cells and to a less extent between the cells of the deeper layers of the mucosa (Fig. 370). The process extends most deeply in those parts of the urethra (penile portion) in which the lining epithelium is of the columnar variety.

Associated Lesions.—In simple cases the disease proceeds no further than has been described, but after a period of several weeks gradually subsides. Very frequently, however, the inflammation extends in

various directions, and complicating conditions arise. Sometimes the infective agents penetrate the *membrana propria* of the small glands (Littre's glands), or enter the submucosa by direct invasion through the interglandular parts of the mucosa. Leukocytic collections in the submucosa or *periurethral abscesses* may result. In these cases the gonococcus alone may be the infective cause, or other pyogenic organisms may be associated; sometimes periurethral lesions are caused by staphylococci independently of gonococci. Occasionally, accumulations of pus in Tyson's glands may simulate periurethral abscesses. In the female, similar purulent distention of the glands of Bartholin is a frequent lesion. The inflammation of the urethra is often confined to the anterior portion (*anterior urethritis*), but may extend to the posterior

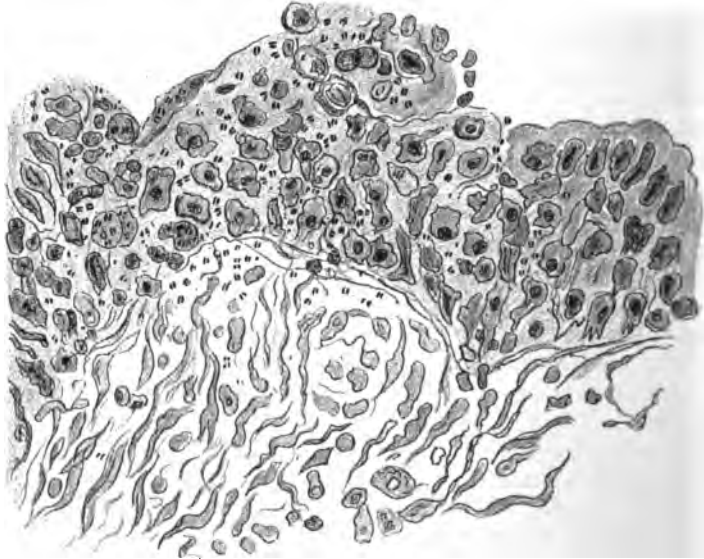


Fig. 370.—Acute urethritis, showing purulent infiltration and gonococci in the cells and between the cells (Birch-Hirschfeld).

portion (*posterior urethritis*). In the male, secondary involvement of the prostate gland is likely to occur with posterior urethritis; and, more rarely, the organisms invade the vas deferens and find their way to the epididymis, causing *acute epididymitis*. The bladder is rarely involved, the mucosa apparently offering considerable resistance to the infection. In the female, acute vaginitis, and especially inflammation of the cervix uteri, are commonly associated. Secondary extension to the uterus may occasion gonorrheal endometritis; more frequently the uterus is but little affected; while the Fallopian tubes suffer intense inflammation. Catarrhal or purulent salpingitis, often complicated with local peritonitis, is one of the most important of the complications. When pus from a gonorrheal urethritis is brought in contact with the conjunctiva a severe form of *purulent conjunctivitis* results.

Metastatic lesions are not infrequent. Among these, *gonorrheal arthritis* is the most familiar. It usually occurs late in the disease, sometimes after an interval of weeks or months from the onset, and involves the larger joints (knee, elbow, wrist). Purulent exudation and fibrous ankylosis may result. A similar lesion is *gonorrheal tenosynovitis*. Sometimes the pericardium, endocardium, and myocardium are involved; and, more rarely, the pleura and the membranes of the cord.

Enlargement of the lymphatic glands of the inguinal region (*bubo*) is frequent; sometimes it terminates in suppuration.

Chronic urethritis is usually the result of continuation of the acute form. It may present itself in the form of a chronic catarrhal process, as a hyperplastic inflammation, or as a productive or cicatrizing form.

In the catarrhal form of chronic urethritis the lesion is practically the same as in the acute disease. The epithelium is loosened and more or less desquamated, and sometimes distinct erosions are observed. Definite ulcerations may occur in parts back of strictures. The columnar epithelium may be converted into the squamous form diffusely or in localized areas. The crypts and glands of the mucosa may be distended with desquamated cells and more or less periglandular inflammation may be observed.

In the hyperplastic variety the mucosa is thickened in a papillomatous manner, and diffuse catarrhal inflammation is associated.

The productive or cicatrizing form is the most important. It may be diffuse in character, but is usually localized and leads to stricture formation.

Stricture of the urethra is most frequent in the membranous portion, but may occur in the anterior parts. Not rarely there are several strictures in the course of the canal. Histologically, the stricture is the result of productive inflammation of the mucosa and submucosa. It is, therefore, a lesion of slow development, and may not become obstructive for months or years after the acute attack of gonorrhea, to which it owes its origin, has subsided. The lumen of the urethra is encroached upon in limited area or for a considerable distance, and, on section, the stricture is found to be hard and resisting. When the lumen of the urethra is greatly narrowed the outflow of urine is impeded, and hypertrophy of the walls of the bladder results. Later, dilatation of the bladder, and even of the ureters and pelvis of the kidneys, may result. The urethra back of the stricture frequently presents the lesions of chronic catarrhal or hyperplastic urethritis, the obstruction serving to prolong the original inflammation of these parts. Rupture of the urethra and extravasation of urine into the cellular tissues, with subsequent necrosis and gangrene, may occur.

In chronic urethritis there is usually a constant but slight discharge of mucous exudate (*gleet*). Examination of this may discover no gonococci or only an occasional group. The urine contains flocculent shreds (*clap-threads*), which on microscopical examination are found to be granular or homogeneous structures resembling cylindroids, and often covered with pus-cells that have adhered to the surface. The

amount of discharge may be quite copious at times, especially in the hyperplastic and catarrhal forms of chronic urethritis.

INJURIES OF THE URETHRA

The urethra may be injured by traumatism from without or within. In cases of falls with injury of the perineum the membranous portion of the urethra may be seriously lacerated, and in women injuries sustained during labor may cause immediate rupture of the urethra, or may first occasion inflammatory and necrotic changes in the anterior wall of the vagina and secondary perforation of the urethra. Injuries from within the urethra may be due to forced attempts at catheterization when some form of obstruction opposes the passage of the instrument. "False passages" are thus occasioned, and may result in fistulæ and extravasations of urine. Concretions or calculi from the kidney or bladder may lodge in the urethra, and may cause immediate perforation or primary inflammation, with secondary rupture of the walls.

Rupture of the urethra causes extravasation of urine into the peri-urethral cellular tissues. If the skin is intact and the urine cannot escape, widespread inflammation, necrosis, and gangrene are liable to occur. Fistulous communications may be established with the exterior, or, in women, with the vagina.

INFECTIOUS DISEASES

Gonorrheal urethritis is the important infectious disease of the urethra. For convenience it has been described under Inflammations.

Tuberculosis of the vesical end of the urethra may be associated with tuberculosis of the bladder. *Lupus* sometimes involves the meatus and anterior end of the urethra in cases of lupus of the external genitalia of women. Very rarely tuberculosis of papillary form is met with in the urethral mucosa.

Syphilis.—The chancre may occur in anterior parts of the urethra in either sex. It usually undergoes rapid ulceration. Mucous patches may occur within the meatus.

TUMORS

The urethra of women is more often the seat of tumors than is that of men.

Small polypoid tumors are occasionally seen hanging from the meatus; they may be fibrous, villous papillomata, or glandular, the latter tending to become cystic.

Carcinoma is usually secondary to cancer of the external genitalia (vulva, vagina, glans penis). Primary carcinoma originating from Cowper's gland has been described, and a few cases of carcinoma of other parts of the urethra have been observed.

Cysts of the mucous membrane, due to retention of the contents of the small glands, are occasionally met with, especially in the posterior portion of the urethra. The inner lining of the cyst is elevated in the form of papillæ covered with squamous epithelium.

Sarcoma of the urethra has been described, but is very rare.

CHAPTER VIII

DISEASES OF THE REPRODUCTIVE ORGANS

THE UTERUS

Development and Anatomy.—The uterus is formed by the fusion of the middle portions of Müller's ducts, the fusion first occurring below where the cervix uteri is developed. The epithelial lining of the ducts gives rise to the mucosa of the uterus, and its outer layers, to the muscularis. The utricular glands are developed by ingrowths from the lining cells, and first appear and reach their most complex development in the cervical portion. The outer surface of the cervix (*portio vaginalis*) is lined with stratified squamous epithelium; the cavity of the uterus and cervical canal, with cylindrical ciliated cells. In the cervical portion are found numerous racemose glands and between them simple tubular glands; in the corpus uteri the glands are simple tubules.

CONGENITAL ABNORMALITIES

Absence of the uterus is very rare. The organ, however, may be represented only by a mass of rudimentary tissue. Hypoplasia of the uterus may be a congenital condition, or may be the result of arrested development and the consequent failure to increase in size at the age



Fig. 371.—Uterus bicornis unicollis (Winckel).

of functional activity. The term *uterus infantilis* is applied. Stenosis and atresia of the uterus and vagina may be the result of disease or maldevelopments, due to partial obliteration of Müller's ducts.

Among the more striking malformations of the uterus are those which result from incomplete fusion of Müller's ducts. In normal development these ducts unite and fuse in the lower portion to form the uterus and vagina, but remain separated above, where they form Fallopian tubes. Among the anomalous conditions of the uterus are *uterus bicornis*, in which the cervical portion of the uterus is single and two entirely distinct uterine cornua are present (Fig. 371); *uterus septus*,

in which the external appearance may be that of a single uterus, but on section a septum is discovered, which divides the organ into lateral halves (Fig. 372); *uterus duplex*, in which there are two vaginas, two uteri, but only two fallopian tubes. The term *uterus unicornis* is used to designate cases in which but one of Müller's ducts has developed, the other remaining rudimentary. Malformations of the vagina may



Fig. 372.—Uterus septus (Cruveilhier).

be associated with those of the uterus already named, though this is rarely the case. A number of subdivisions have been distinguished for each of these malformations, but they are unimportant.

ALTERATIONS OF POSITION

The normal position of the uterus is one of slight anteversion with anteflexion; that is, the fundus lies a little farther to the front than the cervix, and there is a slight bend or flexure in the middle portion.

Anteflexion is a condition in which there is marked angulation of the uterus, the fundus falling forward. Shortness of the round ligaments predisposes to this condition; and it may be caused by the pressure of tumors situated posteriorly, by distention of the rectum with gas, by the traction of adhesions and by abnormal conditions of the uterus itself, causing a loss of tone in the walls. The grade of anteflexion varies greatly. Among the effects of this condition is interference with the discharge of menstrual blood, with consequent accumulation and intense dysmenorrhea.

Anteversion, or the tilting forward of the uterus without abnormal angulation, occurs under similar conditions, but is less important.

Retroflexion of the uterus occurs in cases in which the walls of the uterus are abnormally soft and have lost their tone. It may be caused by the pressure of tumors or the traction of adhesions. Sometimes it is due to habitual constipation, causing pressure upon the lower part of the uterus (cervix) by masses in the rectum; retroversion and subsequently retroflexion are produced. Laxness of the vaginal walls and

rupture of the perineum may cause this or other abnormal positions of the uterus by depriving the organ of its support from below and subjecting it to the unresisted pressure of the abdominal viscera. The degree of retroflexion varies from slight angulation to a complete backward doubling of the organ. The fundus may undergo considerable congestion from the interference with circulation, and it is not rarely enlarged. Adhesions between the uterus and rectum are frequent.

Retroversion is the condition in which the position of the uterus is changed in relation to the pelvis and soft parts, with or without flexion or alteration in the angle of the various sections of the organ itself. The same causes are operative as for flexion, especially prominent being subinvolution.

Lateral displacements of the uterus are rare, and are associated with adhesions or tumors operating laterally.

Upward dislocation may be caused by pressure of tumors in the pelvis; it may be due to the traction of adhesions between the uterus and large tumors of the ovary. In such cases the uterus may be greatly stretched and the vagina may be similarly affected.

Prolapse of the uterus is a term applied to descent or downward displacement. It is possible to distinguish any number of degrees of prolapse, but it is sufficient to speak of two only: *incomplete prolapse*, in which the os uteri is still within the vagina (procidentia); and *complete prolapse*, in which it projects through the vulva, thus partially or wholly everting the vagina. The causes of prolapse of the uterus are numerous. Injuries to the perineal floor and unusual laxity of the vaginal walls or the ligaments of the uterus are very important. Traumatism and excessive pressure upon the uterus from the abdomen may cause descent of the organ, especially if laxity of the ligaments was present before. Retroversion also favors the descent by bringing the uterus into the pelvic axis. Enlargement of the uterus itself may be the cause of prolapse, and in any case the organ usually becomes enlarged after the prolapse, in consequence of passive congestion. The cervix is generally directed somewhat backward, and the mucous membrane frequently presents catarrhal inflammation and contains enlarged veins. The cavity may be filled with considerable mucous secretion.

In some instances of apparent complete prolapse the fundus of the uterus may be but little displaced, the great descent of the os uteri in such instances being due to *hypertrophic elongation of the vaginal portion of the cervix*.

In all cases of prolapse the anterior and posterior walls of the vagina are displaced downward more or less, and sometimes may be completely everted. The anterior vaginal eversion may draw with it the posterior wall of the bladder, and *cystocele* results. Similarly, the posterior vaginal wall may drag down the anterior wall of the rectum, and *rectocele* is produced (Fig. 373).

Inversion of the uterus is a condition in which the organ is turned inside out to a greater or less extent. This condition is caused by traction upon the placenta during rapid labor, or in the presence of lax uterine

muscle, when it is acutely developed; or by the similar traction of polypoid submucous tumors, when it is more slowly formed (Fig. 374). There

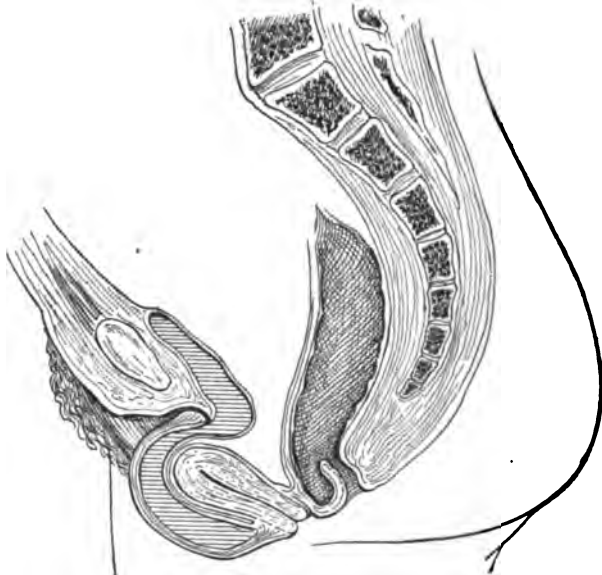


Fig. 373.—Complete prolapse of the uterus (Penrose).



Fig. 374.—Fibroid polyp, producing partial inversion of the uterus (Penrose).

may be only a slight inversion of the fundus, or the organ may be completely inverted and may present itself through the vagina and vulva.

This may be associated with partial or complete prolapse. Secondary changes are apt to occur in such cases. The mucous membrane suffers catarrhal inflammation with ulceration; and the entire uterus, though at first perhaps enlarged by congestion, subsequently atrophies.

STENOSIS, DILATATION, AND RUPTURE

Stenosis of the uterine cavity may occur as a congenital condition, or may be acquired in cases in which inflammation has led to cicatricial stricture. There may be almost complete obliteration of the external or internal os uteri.

Dilatation of the cavity of the uterus is a not infrequent result of stenosis. The dilated cavity may be filled with mucous or seromucous secretion from the non-menstruating mucous membrane (*hydrometra*), or with accumulations of menstrual blood (*hematometra*). Occasionally, in cases of *hydrometra* secondary decomposition of the liquid causes gas formation, and *physometra* results, or suppuration occurs (*pyometra*). In cases of *hematometra* the amount of blood in the uterine cavity may be very considerable, and in some instances rupture of the wall of the uterus is the result. This may be simply due to the increasing pressure, or it may result from inflammation or ulceration at the point of stenosis.

Rupture of the uterus may occur during pregnancy or labor; and occasionally at other times in consequence of inflammations, abscess, softened tumors, and the like. The commonest ruptures are, of course, those in and near the cervical part, but during severe labors, especially of the more difficult presentations, the musculature of the uterus may suffer a longitudinal rent. Disease of the muscle, faulty position of the uterus, which impedes its propulsion of the fetus in the correct axis, favor rupture. The most frequent and serious consequence of rupture is peritonitis. Occasionally, when rupture has occurred during pregnancy, the fetus may be enclosed in a sac formed by circumscribing peritonitis; the rupture may at the same time heal. Subsequently the fetus may be disorganized and discharge through the abdominal wall. This is a very unusual termination.

Laceration of the cervix uteri is a very common accident of labor.

CIRCULATORY DISTURBANCES

Hyperemia of the uterus is a physiological condition during menstruation, and occurs in all forms of acute inflammation of the organ. There is no essential difference between menstrual hyperemia and that of pathological conditions.

Menstruation.—Examination of the mucous membrane during the period shows swelling of the membrane, with multiplication of the interglandular cells and dilatation of the lymphatic channels. The uterine glands are elongated and the cells more or less swollen. Congestion is always conspicuous, and the superficial epithelial cells are desquamated more or less considerably. In the interval between the periods regeneration of the mucous membrane takes place. The term

dysmenorrhea membranacea is applied to abnormal menstruation in which membranous formations are discharged from the uterus (Fig. 375) and in which there is severe pain. The membranes consist of intact portions of more or less degenerated desquamated cells, with or without admixture of fibrin. Cases of this character are particularly prone to occur when chronic inflammations of the mucosa have existed, and the affection is then termed *endometritis exfoliativa*.

Passive hyperemia of the uterus occurs in conditions of general venous stasis, but especially when dislocations of the uterus cause pressure upon the venous plexuses. The organ is enlarged, the veins in the serous surface are prominent, the mucous membrane is dark red, and when the congestion is long continued chronic endometritis may result.

Hemorrhages may occur into the uterine cavity, into the wall of the uterus, or into the peritoneum outside the uterus. Hemorrhages during menstruation and in labor are physiological forms. Pathological increase of menstrual hemorrhage is spoken of as *menorrhagia*, which may occur in certain general diseases, such as anemia, or in consequence of local conditions, notably tumors. Intense congestion of the organ from cardiac disease or from malpositions of the uterus may also lead to hemorrhages during the menstrual period. Hemorrhages between the menstrual periods are spoken of as *metrorrhagia*. This may be caused by general conditions, such as the hemorrhagic diseases and infections (small-pox, etc.), but it is especially frequent as a result of local diseases, of which fibroid tumors and cancer are the most important.

There is a normal hemorrhage from the uterus after detachment of the placenta at parturition which ceases upon uterine contraction, but which may continue in case of imperfect contraction, retained placenta, or diseased uterine vessels.

Hemorrhages into the substance of the uterus are rare and are generally due to traumatism. Apoplexy of the uterus is an interstitial hemorrhage due usually to arteriosclerosis with uterine atrophy.

Hemorrhages into the peritoneal cavities or into the cellular tissues in the vicinity of the uterus are more frequent. Of the intraperitoneal hemorrhages, the most frequent is accumulation of blood in Douglas' pouch (*retro-uterine hematocoele*). The blood in this case may come from various sources, such as ruptured ovarian follicles, ruptured tubes in tubal pregnancy, hematosalpinx, or rupture of varicose veins in the broad ligament. The blood may become absorbed without causing other pathological results, or it may set up inflammation and result in adhesions between the uterus and rectum. Not rarely, perforation with discharge of the blood through the rectum or vagina occurs.

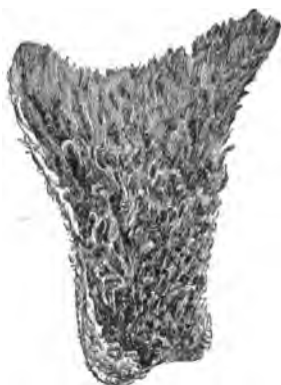


Fig. 375.—Membrane discharged in membranous dysmenorrhea (Penrose).

Hemorrhages into the vesico-uterine pouch and hematmata between the layers of the broad ligament are rare.

INFLAMMATIONS

Inflammation may affect the mucous membrane of the uterus, when the term *endometritis* is applied; or the wall of the uterus, when it is termed *metritis*. The names *perimetritis*, indicating inflammation of the peritoneal covering of the uterus, and *parametritis*, inflammation of the cellular tissues in the vicinity of the uterus, are unnecessary, as these conditions are simply forms of local peritonitis. For purposes of convenience the inflammations of the uterus occurring during the puerperium will be separately considered. Some of the conditions here described as inflammatory are not positively of such nature, though no sharp line of division can be drawn between the inflammatory and the hyperplastic forms.

Acute catarrhal endometritis may result from traumatism, or from infection with pyogenic organisms or gonococci. Occasionally it occurs as a complication of general infectious diseases, such as typhoid fever and cholera. The mucous membrane is swollen and intensely hyperemic; very often small hemorrhages are observed. Desquamation of the epithelial cells, with mucopurulent secretion, causes considerable discharge. In most cases the body of the uterus is affected, but in the gonorrheal form the cervical portion is the most frequent seat. Very intense forms may occasion necrosis of the epithelial cells and the formation of pseudomembranous deposits. This is particularly frequent in the infectious diseases.

Chronic endometritis may be the continuation of acute endometritis, and is especially apt to occur in persons of reduced vitality, such as scrofulous or chlorotic women, or in those in whom the circulation is sluggish. The influence of passive congestion has already been referred to. Very often the etiology is entirely obscure.

The mucous membrane in the earlier stages is simply swollen, and produces abundant mucopurulent secretion. Later, hyperplastic changes occur, the hyperplasia affecting either the uterine glands or the interstitial tissue. The terms *endometritis glandularis* and *endometritis interstitialis* have been applied to distinguish these varieties. In the former, microscopical examination shows an abundance of proliferated glandular acini extending through the depth of the mucous membrane (Fig. 376). In the latter the glands are less conspicuous, but round-cell infiltration and abundant connective-tissue hyperplasia between the glands are conspicuous features (Fig. 377). In some of the cases, particularly in those of the glandular form, the process seems more closely allied to tumor formation than to inflammation; and it is very difficult to draw a sharp line between some forms of adenoma and sarcoma of the mucous membrane on the one hand, or chronic inflammations on the other, in attempting which, one should remember that the glandular layer lies immediately upon the muscle, so that acini as deep as the muscle-bundles do not necessarily indicate malignancy.

The mucous membrane may in the advanced stages be considerably swollen and project in a polypoid form (Fig. 378). Later, atrophy may take the place of hypertrophy, and in some instances the lining epithelial cells lose their cilia and change their character from the typical columnar

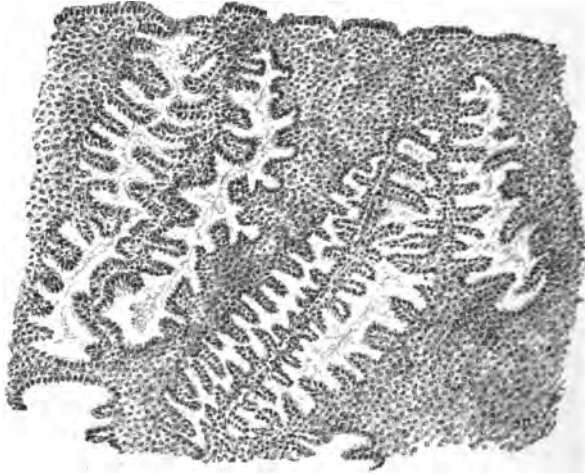


Fig. 376.—Glandular endometritis.

cells to a distinct squamous type. The small glands of the membrane may be obstructed at their mouths and cystic distention may result. This is particularly conspicuous in the case of the Nabothian glands of

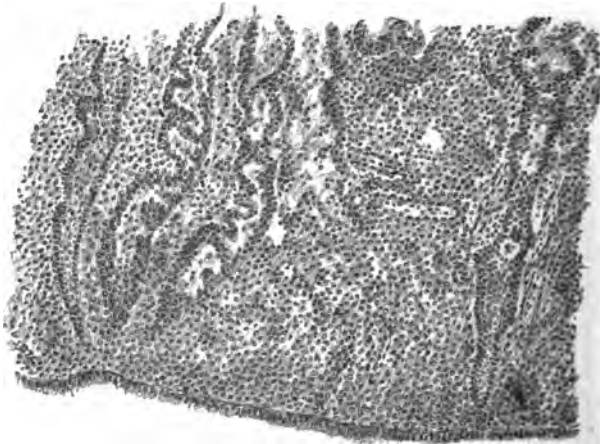


Fig. 377.—Interstitial endometritis.

the cervix, and retention cysts of these glands may reach the size of a pea or a small cherry. Occasionally, erosions or slight ulcerations are met with in cases of chronic endometritis.

Chronic endometritis of the cervix is frequently secondary to in-

inflammations of the vagina, and may be due to gonorrheal infection or other causes. The mucous membrane of the cervical canal is greatly thickened, and may project from the os uteri (ectropium). Retention

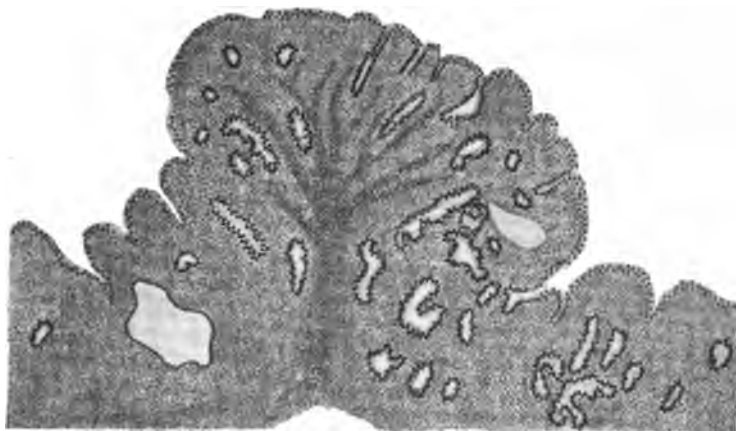


Fig. 378.—Polypoid endometritis (Penrose).

cysts of the Nabothian glands are sometimes a conspicuous feature, and cystic mucous polyps are not unusual.

The tears and erosions incident to repeated pregnancies, especially if any be mechanically delivered, combined with hyperemia from uterine malpositions, favor chronic endocervicitis.

Chronic endometritis may lead to chronic metritis, or by extension may occasion tubal disease. Clinically, it is characterized by more or less constant mucopurulent discharge.

Erosions of the uterus are especially frequent in the cervix; they result from endometritis. The mucosa within the cervical canal undergoes hyperplastic changes and projects from the os uteri in a polypoid form. Between the papillomatous projections cystic formations may develop, and these may rupture, leaving exposed ulcerations. Granulation tissue is developed and sometimes becomes exuberant in character.

The term "erosion" is also applied to areas in which the normal squamous epithelium of the cervix has become converted into cylindrical, or in which the cylindrical epithelium of the body of the uterus has extended downward to the cervix. Other erosions are due to lacerations of the cervix (Fig. 379), and occasionally congenital erosion has been observed.



Fig. 379.—Left lateral laceration of the cervix, with erosion (Penrose).

Phagedenic ulceration of the cervix has been described as an independent disease. Some of the cases are undoubtedly instances of ulcerating carcinoma; in other cases ulcerations in this situation have been met with in which microscopical examination showed no evidence of carcinomatous tissue.

Acute metritis is rarely met with except during the puerperium, but may be the result of acute endometritis. The wall of the uterus becomes thickened, soft, and edematous. Occasionally purulent infiltration is observed.

Chronic metritis frequently occurs in the puerperium as a result of retarded involution of the uterus. It may be occasioned by chronic congestion of the uterus, or may be secondary to chronic endometritis. The uterine wall is infiltrated with round cells, and the connective tissues undergo active hyperplasia, which in the later stages leads to great thickening and induration. Coincidentally, there is usually some hypertrophy of the muscular elements themselves. It is by no means certain that all of the cases grouped under this term are inflammatory in nature. Some are certainly more closely allied with diffuse tumor formation. The mucous membrane is usually thickened, and becomes secondarily involved if it was not primarily diseased. The peritoneal covering may be similarly affected, and chronic perimetritis with adhesions of the uterus results.

INFECTIOUS DISEASES

Puerperal Infections.—This term may be applied to various forms of infection occurring during the puerperium, but in the majority of instances the streptococcus is the specific organism.

Etiology.—Two important factors are concerned: (a) Injuries to the surface of the uterus, vagina, or vulva; and (b) some form of infection. The more or less denuded surface of the uterus offers a ready entrance to micro-organisms, as well as an absorptive surface for soluble poisons produced by micro-organismal decomposition within the uterus; and infection may take place without any further injury than that occasioned by the normal processes of labor. In most instances, however, there is actual injury either of the surface of the uterus, cervix, vagina, or vulva, and the micro-organisms or poisons are admitted through these wounds. There may be primarily, however, more than a simple injury of the mucous surface. In consequence of prolonged pressure necrotic lesions terminating in gangrene may first be established, and from this secondary infections may take place. In cases in which infection occurs without injury to the walls, as well as in cases in which injury has been sustained, the pathogenic organisms may first find a lodgment and multiply within blood-clots or retained secundines within the uterus; and the organisms or their toxic products are secondarily admitted to the uterine tissues.

Puerperal infection is probably in most cases the result of the entrance of micro-organisms from without, and may be traced to want

of cleanliness on the part of the accoucheur or the surroundings. Sometimes widespread epidemics have been caused by the carelessness of a single obstetrician, whose hands perhaps had become infected from operating upon or examining cases of erysipelas, general pyemia, or the like.

Among the micro-organisms, as has already been stated, the *Streptococcus pyogenes* is most important. Staphylococci of various sorts, bacilli resembling the *Bacillus coli communis*, the bacillus of tetanus, gonococci, and other organisms occasionally infect the puerperal uterus, but in these instances the pathological conditions are different from those met with in ordinary puerperal infection, which may be considered as practically always a streptococcic infection.

Pathological Anatomy.—In most instances there is primarily a lesion upon the mucous surface of either the uterus, the vagina, or the vulva. The nature and extent of this depend upon the amount of injury occasioned during labor. In some instances the lesion is trivial in extent, and remains so, though widespread infection results from it. In most cases, however, there is a rapidly spreading inflammation of the endometrium or mucosa of the vagina, and pseudomembranous deposits are very frequently met with upon the surface. Necrotic and gangrenous changes in the mucous membrane are most pronounced in cases in which prolonged pressure has been exerted by the head in its descent or by instruments.

The extension of the infection may occur in two ways, either through the blood-vessels or through the lymphatic channels; and the local and general lesions vary correspondingly.

In cases in which the infection spreads along the blood-vessels there may be primarily septic softening of the thrombi within the uterus and purulent phlebitis of the venous channels at the placental site. Thrombosis extends from this situation through the veins to the various plexuses in the vicinity, and infected emboli are carried through the circulation to distant organs, such as the lungs, the kidneys, and the spleen. Metastatic abscesses and inflammatory swelling of the affected organs result. The kidneys in particular are often the seat of numerous punctate or miliary abscesses.

In the cases in which extension occurs along the lymphatic channels the uterus is enlarged, soft, and often pultaceous. Streaks or lines of light color may be observed running from the mucous surface toward the periphery. These represent the lymphatic vessels filled with purulent exudate. The walls of the lymphatics may be penetrated, and perilymphangitic abscesses are thus occasioned. When the process has extended to the lymphatics in the outer layers of the uterus, phlegmonous inflammation of the subperitoneal tissues (parametritis) results, and finally the peritoneum itself may be involved.

The spleen is enlarged, though less decidedly than in the form in which infection occurs through the blood-vessels.

Extension along the mucous membrane itself may lead to associated disease of the tubes; more frequently the tubes are invaded at their abdominal end after peritonitis has developed.

Puerperal sepsis is peculiarly virulent and rapid in its course, and may occasion widespread changes in all of the tissues of the body.



Fig. 380.—Diffuse tuberculosis (ulcerative and caseous) of the endometrium (Kaufmann).

Tuberculosis of the uterus is most frequently met with in the mucous membrane of the uterine body, and is usually secondary to disease of the tubes. Direct infection may possibly occur through coitus, but is certainly rare. The disease occurs in the form of a nodular or diffuse infiltration with a tendency to rapid ulceration or caseous necrosis involving the mucous membrane and to some extent the submucosa. The entire cavity of the uterus may be covered with caseous and necrotic deposits (Fig. 380). In the later stages the process may extend deeply, even involving the muscular layer of the organ. The cervix is rarely attacked. Sometimes miliary tubercles are found in the uterine mucosa without marked degeneration (Fig. 381).

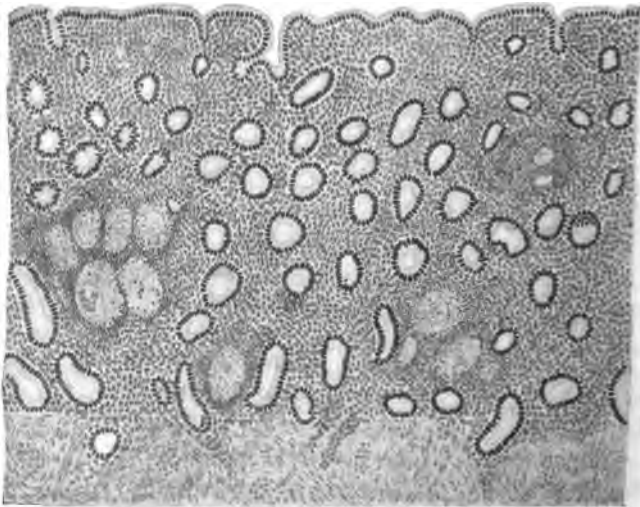


Fig. 381.—Miliary tuberculosis of the endometrium and glandular endometritis (Beyea).

Syphilis of the cervix uteri may occur in the form of a chancre, a condyloma, or as tertiary infiltration, but active lesions of the body are rare, although it is infected as indicated by syphilitic placentas and fetuses.

ATROPHY AND DEGENERATION

Puerperal Atrophy.—The uterus suffers a most remarkable atrophy following labor. This proceeds very rapidly at first, and then more slowly; and under favorable conditions the organ resumes its previous condition in the course of a few months. The muscular fibers decrease progressively, from their previous hypertrophied condition in which they frequently attain a length and diameter three times the normal, until, at the end of involution, the usual size and appearances are attained. Many muscle-fibers undoubtedly are destroyed. The process of involution is really one of fatty degeneration.

Senile Atrophy.—The uterus undergoes progressive atrophy at and after the period of the menopause, and finally becomes greatly reduced in size. The substance of the organ may undergo a progressive sclerosis, or in other instances becomes softer than normal. Catarrhal endometritis is often associated, and the columnar cells are sometimes converted into squamous epithelium.

Fatty degeneration, independent of that which occurs during puerperal involution, is a rare condition, but may occur in the course of certain infectious diseases, such as typhoid fever, or may result from the action of the parenchyma poisons.

Amyloid infiltration is rare and unimportant.

HYPERTROPHY AND HYPERPLASIA

Hypertrophy of the entire uterus may occur in association with inflammation or metritis, or may result from chronic congestion of the organ. The enlargement in cases usually designated as hypertrophied is, for the most part, due to new formed connective tissue. True hypertrophy occurs as a physiological process during pregnancy. In this variety the muscle-fibers increase enormously in size, and doubtless also multiply their number. The blood-vessels and connective tissues undergo corresponding hypertrophy.

Hypertrophy of the cervix uteri is occasionally met with independent of hypertrophy of the uterus as a whole. It may be caused by chronic irritations of the cervix, as in cervical endometritis, or may result from obscure causes. Frequently it is met with in prolapse of the uterus, and sometimes its elongation simulates prolapse.

Hyperplasia of the mucous membrane of the uterus has been referred to in the discussion of Chronic Endometritis. In some instances that are designated as endometritis the pathological process seems to be rather of a purely hyperplastic character, and more closely allied to tumor formation than to ordinary inflammation. In these cases the mucous membrane in all parts of the uterus may be greatly thickened, and may suffer more or less papillomatous transformation. Sometimes limited portions are affected, and polypoid formations result.

Polypi of the uterus may be of various sorts. Very commonly they present themselves as simple mucous polypi, due to projection of

parts of the mucous membrane; in other cases secondary changes, such as cavernous dilatation of the blood-vessels or cystic transformation of the small glands contained in the polyp, occasion marked variations from the original appearances. Myofibromata, sarcomata, and other forms of tumors originating in the mucous membrane or just beneath it may assume a polypoid appearance.

TUMORS

Leiomyoma; Myofibroma; Fibroid.—The tumors of the uterus designated by these terms are in nearly all cases composed of smooth muscle-fibers and fibrous tissue, and from the pathological standpoint the term “myofibroma” is, therefore, most applicable. There are many grades of combination in these tumors. Beginning with the soft red, illly outlined tumor composed almost entirely of muscle-cells, they pass into forms of paling color and increasing consistency to the almost stony



Fig. 382.—Interstitial fibroid tumor of the uterus: a small submucous fibroid appears in the uterine cavity (Penrose).

hard fibroid mass, which shows either no muscle-cells or only the fattily degenerated remains thereof. They present themselves in the form of rounded and usually well-circumscribed masses, from the size of a grape-seed to that of tumors weighing 40 or 50 pounds. They are generally multiple, and on section have the appearance of concentric or irregular lamellæ. Microscopically, the tumors are composed of smooth muscle-fibers and of fibrous tissue arranged in bundles or layers running in various directions. The muscle-fibers are frequently found arranged concentrically about small blood-vessels, and in some instances the vessels are telangiectatic.

Secondary changes are very common, the most frequent being calcification. This may begin either in the center or at the periphery, but more commonly it is diffuse. Edema of the tumor may cause it to

become quite soft, and cystic transformations due to softening or to distention of the lymphatic spaces are sometimes observed. Inflammation may arise and myxomatous or sarcomatous change is known.

Several varieties have been distinguished, according to the seat of the tumors. In some instances they are embedded in the wall of the uterus, when the term *interstitial* or *mural fibroids* is applied (Fig. 382). In other cases they arise in the uterine walls just beneath the mucous membrane, when they are called *submucous fibroids*. These may gradually project into the cavity of the uterus as *fibroid polypi*. In the third group of cases the tumors have a *subperitoneal* location, and may project from the outer surface of the uterus as knobbed masses (Fig. 383), which may become pedunculated. In rare instances they extend between the layers of the broad ligament. Fibroid tumors are benign in a pathological sense, but occasion serious disturbances either by pressure

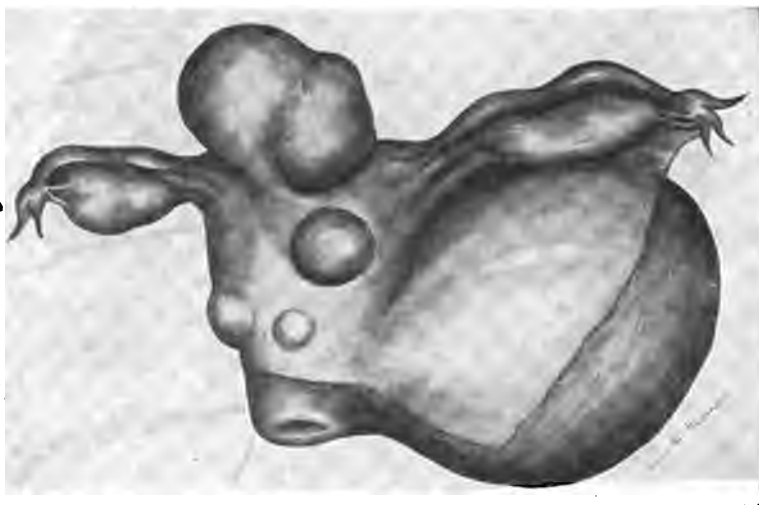


Fig. 383.—Subperitoneal fibroids and an intraligamentous fibroid of the uterus (Penrose).

or by the metrorrhagia and endometritis to which they frequently give rise. Subperitoneal fibroids may become free bodies in the peritoneal cavity, and the submucous form is sometimes discharged from the uterus after a spurious labor. The so-called *adenomyoma* and *adenofibroma* are tumors including some epithelial structures as nests or cystic glands. They are due most likely to a downgrowth of the superficial epithelial structures, but it has been maintained that they are due to remnants of Wolffian body. Some persons view them as results of inflammation. They do not grow like simple adenomata nor behave like malignant adenomata (Fig. 384).

Sarcoma of the uterus may arise from the muscular layer or from the endometrium. That arising from the myometrium is usually associated with myoma and fibroma. In some cases the sarcomatous elements of the tumor are developed in a pre-existing myofibroma. In

other cases the sarcoma and fibroma are coincidentally formed. These tumors differ from typical fibroids in being more rapid in growth, less well circumscribed, softer, and more homogeneous in appearance. Sometimes they are situated just beneath the endometrium, and become converted into *sarcomatous polypi*.

Sarcoma of the endometrium may occur in a circumscribed or papillomatous and in a diffuse form, the latter involving the entire mucous membrane of the organ. The papillomatous variety is soft and villous and highly vascular. In some cases the structure is that of



Fig. 384.—Cystic fibro-adenoma of uterus.

angiosarcoma. In the diffuse form the entire cavity of the uterus may be filled with soft villous projections from the mucous membrane.

A special form of sarcoma has been described as occurring in the vaginal portion and cervix. In this the tumor has a grape-like structure, and, microscopically, consists of myxomatous tissue with areas of sarcomatous character. It occurs in young persons, even in childhood.

Syncytioma Malignum.—(See p. 238.)

Adenoma may occur in the form of polypoid outgrowths from the mucous membrane, or as a diffuse process not readily distinguishable from that commonly designated as endometritis glandularis. Both of these forms are benign.

Malignant adenoma usually arises from the corpus uteri, and presents itself as a soft, irregular elevation of the mucous membrane in a

localized area, or diffusely involving a large part of the endometrium. It tends to spread through the walls of the uterus, invading the myometrium (Fig. 385), and finally penetrating to the peritoneal covering, where

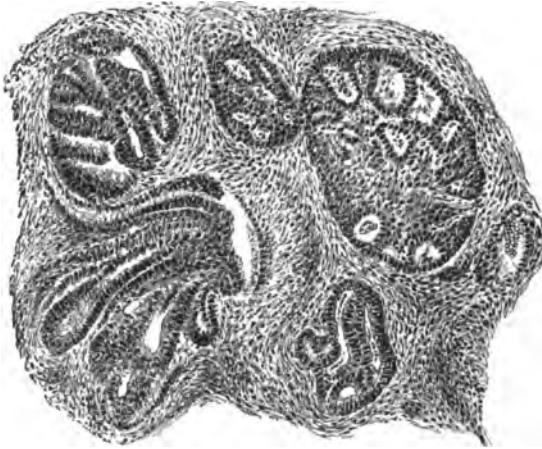


Fig. 385.—Malignant adenoma. the section is taken from the deeper parts of the tumor, and shows the invasion of the myometrium.

secondary nodules may develop. Histologically, it is characterized by the production of atypical, branched, intercommunicating, or cyst-form-

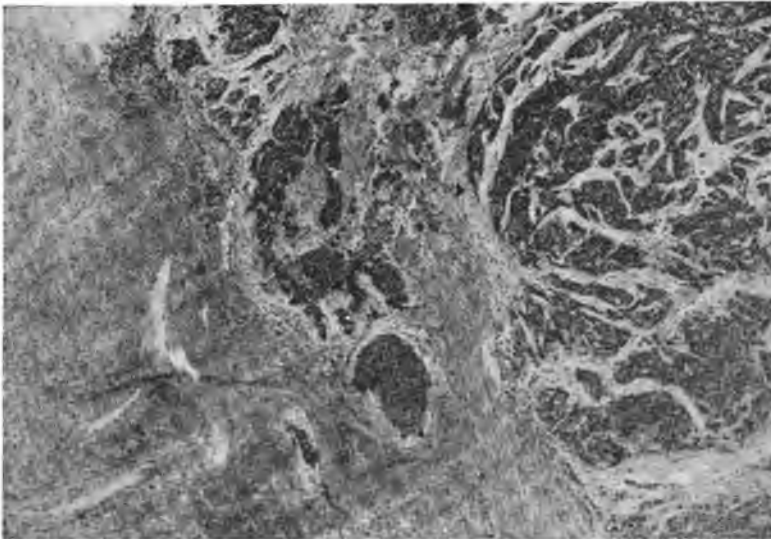


Fig. 386.—Carcinoma cervicis uteri, showing penetration of nests into muscle.

ing gland-acini with comparatively little stroma, the latter being of soft fibrous character. The tumor is malignant in its tendency to invade the wall of the uterus and neighboring structures, and it may

become converted into actual carcinoma in the later stages. In such instances the acini in places show a heaping of epithelial cells and a tendency to destruction of the basement-membrane, with proliferation of the cells in the stroma.

Carcinoma is the most frequent of the malignant diseases of the uterus, and usually invades the cervical portion; more rarely it arises from the corpus uteri. Carcinomata starting on the vaginal surface of the cervix are squamous-celled epitheliomata; those originating in the cervical canal and in the corpus uteri are tubular or glandular carcinomata.

Carcinoma of the portio vaginalis usually begins from the inner surface of one of the lips of the os uteri, and causes a firm infiltration of the affected portion, the disease penetrating into the submucosa and muscularis.



Fig. 387.—Diffuse cancer of the endometrium (Penrose).

Subsequently, ulceration takes place, and the diseased area becomes converted into an elevated and irregularly ulcerated surface. Extension may take place to the vaginal walls and to the tissues surrounding the cervix uteri (Fig. 386). Ulceration may establish communications between the vagina and bladder or rectum. Extension upward into the supravaginal portions of the cervix and to the corpus uteri may occur through the lymphatic channels, or by direct invasion. Secondary involvement of the lymphatic glands of the iliac, lumbar, and inguinal groups is frequent.

Instead of the usual indurated and ulcerating form, cervical epithelioma may present itself as a cauliflower-growth—that is, as a destructive or malignant papilloma. In such cases it is likely that the growth often begins as a papilloma, causing irregular elevations, and that the penetration into the tissue at the base of the growth is a secondary development. In the later stages this form, like the preceding, undergoes ulceration. Both varieties, but particularly the latter, frequently cause uterine hemorrhages.

Carcinoma of the corpus uteri and of the cervical canal develops from the tubular and racemose glands of the mucous membrane. It may begin as an adenomatous growth, subsequently becoming transformed into carcinoma. Macroscopically, the growth presents itself

as a villous or papillomatous thickening of the mucosa, either localized or diffuse (Figs. 387 and 388). In the later stages considerable involvement of the wall of the uterus occurs, and even perforation may take



Fig. 388.—Cancer of the body of the uterus: a large, single cancerous nodule in the anterior wall has been divided (Penrose).

place. Microscopically, the usual appearances of glandular cancer or adenocarcinoma are discovered (Fig. 389).



Fig. 389.—Glandular cancer of the cervix uteri.

Squamous epithelioma is met with in rare instances in the corpus uteri, especially in women of advanced years. The explanation of this growth is that it arises from epithelium that has undergone a

change from the customary columnar to the squamous form, in consequence of chronic endometritis.

Cysts.—Small cysts of the wall of the uterus may be associated with various forms of tumors, such as myofibromata; and a form of adenocystoma, probably originating from remnants of the Wolffian duct, has been described. Dermoid cysts have been occasionally observed.

PARASITES

Echinococcus cysts are sometimes met with, and a few cases of supposed *Cysticercus cellulosæ* have been described, though the nature of the formations was uncertain.

THE OVARIES

Development and Anatomical Considerations.—The ovary and testis are developed from a primary indifferent sexual gland, which is indistinguishable in the two sexes. This indifferent gland is formed on the ventromesial surface of the Wolffian body by a localized thickening of the mesothelial elements. The ovarian stroma is subsequently formed by ingrowths of the surrounding mesoderm. The ovary consists of a stroma of peculiar spindle-shaped connective-tissue cells. In the central or medullary portion the tissue is highly vascular; the peripheral or cortical part contains abundant Graafian follicles in which the ova are developed. These follicles are formed from primary tubular indentations of the cuboidal or columnar epithelium that covers the organ. These indentations are the tubes of Pflüger. After full development of the ovary they are wanting, the greater part, by constriction of the deeper portions, having formed primordial follicles. The *paroöphoron*, a vestigial structure, is the part of the ovary at the hilum. It consists of connective tissue and blood-vessels with a number of parallel tubes which are remnants of the Wolffian body. The same tubules surrounded by connective tissue extend outward between the layers of the broad ligament, constituting the *parovarium*. Sometimes part of the Wolffian duct remains patulous and constitutes the duct of Gärtner. This is the homologue of the vas deferens.

CONGENITAL ABNORMALITIES

Occasional *absence* of one or both ovaries has been discovered with other developmental defects, or independently. *Hypoplasia* occurs in chlorosis, and occasionally in association with other conditions. Sometimes *supernumerary* ovaries have been found. The additional ovaries may be formed by division or by separation from one of the normal glands.

CHANGES IN POSITION

More or less extensive dislocations of the ovaries may occur, the most notable being that in which one of these organs descends into a hernial sac, occupying either the inguinal or crural canal. Dislocations resulting from pressure, adhesions, and the like are frequent.

CIRCULATORY DISTURBANCES

Active hyperemia, or congestion, may be either a physiological or pathological condition. The former occurs during the menstrual period, the latter in association with inflammation of the neighboring structures or in the earlier periods of inflammation of the ovaries themselves.

Passive congestion is met with in chronic cardiac diseases, and as a result of local obstructions to the circulation by tumors, inflammatory adhesions, torsion of the tube, and uterine displacements.

Hemorrhage.—Small hemorrhages into the ovarian tissue are very frequent. Their occurrence is usually sufficiently accounted for when the functional activity of the organ is considered. At each periodical ovulation a small follicle ruptures, to discharge the contents containing the ovum. Generally there is a slight extravasation of blood at such times, which is subsequently absorbed. At the same time that the extravasation and absorption are taking place the inner lining of the follicle proliferates somewhat, and the cells then undergo fatty degeneration. The whole process gives rise to a yellowish nodular formation, termed the *corpus luteum*. Subsequently this is removed by absorption of the blood and by degeneration and absorption of the proliferated cells of the lining membrane, and a small scar alone remains. The latter, especially when more than usually fibrous, is known as the *corpus fibrosum*. This is commonly a little pigmented, in consequence of the pre-existing extravasation of blood. The corpus luteum, which is developed from a follicle formed at the time of impregnation (corpus luteum of pregnancy), differs somewhat in character. The epithelial proliferation is much more active, and the wall of the follicle is intensely congested. Rapid involution does not take place, the follicle often persisting for considerable periods after the termination of pregnancy, and acting, according to some writers, as a glandular organ with an internal secretion having an inhibitory effect upon further ovulation, but inciting activity in the mammæ.

Exceptionally, considerable hemorrhages may take place into the follicles, and small hemorrhagic cysts or cysts containing blood-stained liquid may be formed.

INFLAMMATION

Inflammation of the ovaries, or oöphoritis, is generally a secondary condition resulting from an extension of inflammation from the neighboring reflections of the peritoneum, or from extension of infective processes along the Fallopian tube. The extension from the neighboring peritoneum, as well as from the uterus, may be direct—that is, along the planes of tissue or through the lymphatic or vascular channels. Acute oöphoritis is not infrequent in various forms of general infection, such as typhoid fever, pneumonia, influenza, etc. Primary oöphoritis is probably very rare.

The ovary becomes enlarged, and in the earlier stages is more or less congested. Later, the tissues become yellowish, either uniformly or in

scattered areas. Finally, the process may terminate in necrosis or abscess formation. Since such purulent collections either extend or perforate into the tube, *tubo-ovarian abscesses* arise. Such ovarian abscesses may reach a considerable size, and break into any of the hollow viscera near by or into the peritoneal cavity. In more favorable cases there are only small collections of pus, and these may subsequently become inspissated. The most satisfactory of all terminations is in complete resolution or in induration (*chronic oöphoritis*). The ovary in chronic oöphoritis may show the changes most upon or near the surface, a condition which leads to fibrous adhesions to the peritoneum. Cysts in the cortex are common, due to prevention of rupture of the Graafian follicles. The organ in chronic inflammation, except where cysts are numerous or large, is small, white, and quite firm.

Localized inflammations may sometimes occur about the follicles. These may terminate in follicular abscesses, which either discharge and lead to scar formation or become inspissated.

INFECTIOUS DISEASES

Tuberculosis.—Among the infectious diseases, tuberculosis alone is of importance. It may arise as a primary disease of the ovaries, but much more frequently is secondary to inflammation of the tubes or other parts of the genital tract. It may give rise to the formation of small or large cheesy masses, showing a tendency to softening with formation of tuberculous abscesses. The ovaries may occasionally be the seat of miliary tuberculosis.

TUMORS

The ovaries are frequent seats of tumors, both benign and malignant. By far the largest proportion are cystic.

Connective-tissue Tumors.—*Fibromata* may occur as small nodular growths, either single or multiple. In some cases the tumors are of considerable size. Combinations of fibroma with leiomyoma may also be met with; these *myofibromata* resemble those of the uterus. Occasionally *fibrosarcoma* is encountered. *Chondroma* is a rare form of benign tumor, usually teratomatous in nature.

Sarcoma may occur in the form of spindle-celled sarcoma, fibrosarcoma, or, more rarely, as round-cell sarcoma. It appears as a rounded tumor with more or less pronounced encapsulation. Degenerations, such as myxomatous, are not infrequent, and cystic change may be occasioned by dilatation of the follicles. In some cases proliferations of the walls of the follicles constitute an important part of the growth. To such cases the name "adenosarcoma" may be applied.

The ovary is a favorite seat of mixed tumors, most of which are teratomatous and fall into two classes, solid and cystic, of which the latter are more common and important. All sorts of combinations among the benign and malignant growths, or mixtures of these, have been seen. The benign tumors, especially if cystic, are prone to undergo malignant change.

Cystic Tumors.—Of the cystic conditions of the ovary we must distinguish the *simple follicular cysts*, and the more important *myxoid* or *colloid cystomata* and *dermoid cysts*. Of the cystomata, there are two varieties—the papillary and the glandular.

Follicular cysts are developed by distention of the Graafian follicles with dropsical liquid. The ovary may be considerably enlarged by cystic cavities, lined with epithelium, and containing clear watery liquid or, occasionally, blood-tinged contents. Cysts of this character are very common in cases of induration of the ovary following oöphoritis. One form of this follicular cyst formation is so extensive that it seems as if all the potential Graafian follicles had attempted to ripen and had filled up with clear fluid. This is the “cystic degeneration of the ovary,” and forms a large cystic mass with little organ tissue remaining.

Colloid or myxoid cystomata present themselves as tumors of small or large size, having a tendency to a multilocular cystic character. The cavities are filled with a more or less gelatinous or mucoid liquid. Sometimes hemorrhage takes place, and the contents are correspondingly altered. Two subvarieties may be distinguished: the glandular and the papillary.

Glandular cystomata are distinguished by the constant proliferation of the epithelial elements in the form of acini. This occasions a multilocular character, new cysts springing from the walls of the original cavity or appearing within the substance of the primary tumor. The terms *adenocystoma* and *cysto-adenoma* are appropriate. The tumor may present itself as a large, single, rounded, unilateral or bilateral cyst with insignificant projections of small cysts upon the inner lining; while in other cases there is found on section a uniform multilocular character. Microscopically, the characteristic feature of these tumors is the formation of regular gland acini, showing a single layer of epithelial cells, or at most a few layers resting upon a basement-membrane, the lining showing a tendency to sprout from or sink into the wall, in either case to form new cysts. The stroma of the tumor is composed of fibrous connective tissue, with some unstriped muscle-fibers. The contents of the cysts have the mucoid or colloid character referred to, and chemically a substance is discovered that is absent from simple follicular cysts of the ovary and is less abundant in papillary cystomata. This substance is termed “pseudomucin” or “paralbumin,” and is somewhat related to mucin. Occasionally, when the cysts are old, the contents may be quite watery.

Cystomata soon destroy the ovary, the unaffected ovarian tissue being spread out within the wall of the cyst. The tumor is attached in the pelvis by a pedicle consisting of the broad ligament and Fallopiian tube, and often forms secondary inflammatory adhesions to adjacent parts.

Glandular cystomata arise either from embryonal rests (Pflüger's tubes) or from ingrowths of the surface epithelium of the organ. It is generally considered unlikely that they arise from Graafian follicles.

Papillary Cystomata.—Papillary cysts occur in two forms, the one

closely resembling glandular cystoma in its general appearance, the other presenting itself as a papillomatous condition of the surface of the ovary (Fig. 390). In the former, or papillary myxoid cystomata, large



Fig. 390.—Papillary adenoma of ovary.

cystic tumors are developed. On section through these there is found a papillomatous or cystic proliferation of the lining membrane, but the tendency to the formation of secondary cysts is much less pronounced



Fig. 391.—Double papillomatous cyst of the ovary: the right cyst has ruptured and is turned inside out, showing a mass of papillomata; papillomata have penetrated the wall of the cyst; the peritoneum has been infected, and a papillomatous growth appears on the fundus uteri (Penrose).

than in the glandular varieties, and the fibrous stroma is less abundant. The secondary cysts in this variety may be formed by fusion of the free ends of proliferating papillæ, or by myxomatous degenerations within

the stroma of the papillæ. The liquid of the cysts resembles that of the glandular form, but contains less pseudomucin, and is more frequently hemorrhagic. On microscopical examination it is found that the inner lining of the cyst and the papillary projections consist of stratified ciliated epithelium. Calcareous bodies arranged in a concentric fashion (psammoma bodies) are frequently met with in the stroma, as well as in the epithelium. The same calcareous bodies are occasionally found in glandular cystomata.

The papillomatous ovarian tumors differ from the glandular in being almost invariably bilateral (Fig. 391). Their origin has not as yet been certainly determined, but it is probable that they originate from the paroöphoron, a vestigial remnant of the parovarium. Some have held that they may originate from the Graafian follicles or from ingrowths of the surface epithelium. This is assuredly not a frequent origin.

The surface papillomata of the ovary present themselves as irregular masses of a cauliflower appearance. The papillary projections are covered with cylindrical epithelium, as in the cystic form. There is no essential difference in structure, and it is probable that in many instances the superficial forms result from a rupture of the cystic variety and the subsequent external proliferation.

The papillomatous cystomata and the surface papillomata have a marked tendency to carcinomatous transformation, and tend to spread to the peritoneum, causing metastatic nodules in the vicinity or throughout the entire abdomen.

Both these cysts, especially the former, give rise to the so-called "pseudomyxoma peritonei" when they rupture. The latter cyst is more malignant than the former, as it can infiltrate through the cyst wall and extend by continuity. Frank carcinomatous change is possible with metastases in distant organs.

Dermoid cysts are frequently met with in the ovary. They may occur as small nodules or as very large tumors, and are usually unilateral. The larger ones substitute the ovarian tissue completely; less commonly they may be pedunculated, the ovary in part remaining intact. Combinations with glandular cystomata are not infrequent.

The dermoid cyst is a smooth-walled sac, the inner surface presenting somewhat irregular projections and having more or less pronounced characteristics of epidermal tissue. The cystic contents are a putty-like material of grayish color, containing long blonde hairs and teeth, and sometimes ill-developed bone. The grayish material consists of fatty detritus containing degenerated epithelial cells, and usually abundant cholesterin crystals. The wall of the dermoid cyst, though usually in the main composed of epidermal structure, may contain elements of the three blastodermic layers. The dermoid cyst may occur in childhood or even in fetal life, but usually does not present itself until adult years.

Secondary changes not infrequently occur. Inflammatory conditions of the walls may occasion abscess. Sometimes the epithelium proliferates actively, and the dermoid, in part or as a whole, is converted into a carcinoma.

Carcinoma of the ovary may be a primary growth of glandular character developing from the follicles, or it may be of a mucous or colloid variety, when the ovarian tissue becomes converted into a gelatinous mass. In the latter case the tumor tends to spread to the adjacent peritoneum, and widespread metastasis along this membrane may occur.

Mention has already been made of the carcinomatous change in cystadenomata. When such metamorphosis occurs one finds distinct epithelial cell nests besides the proliferating and atypical gland cavities. The solid cancers of the ovary are usually of the medullary type, but connective tissue may be prominent.

Secondary tumors of the ovary, usually carcinomatous, are not common, yet when they occur frequently attain great size, out of proportion to what might be expected from the size of the original mass. They may be multiple. Metastasis is commonest from the mammæ, stomach, and rectum, usually by the hematogenic route or through the peritoneum.

CYSTS OF THE PAROVARIIUM

Cysts of the parovarium may be considered in this place on account of their clinical resemblance to ovarian cystomata (Fig. 392). They are distinguished, however, by their intraligamentous situation, by their

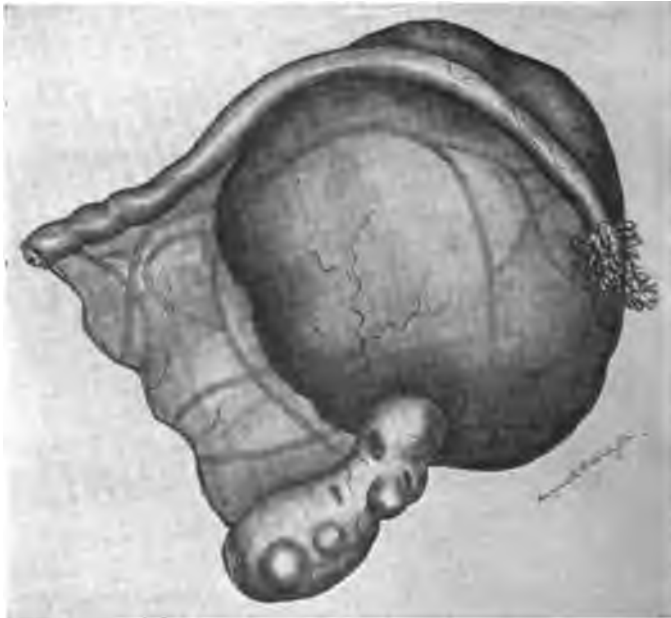


Fig. 392.—Cyst of the parovarium: there is no distortion of the ovary; the Fallopian tube has been much elongated.

almost invariably unilocular character, and usually by their clearer and more serous liquid contents. The ovary is usually uninjured. The inner lining consists of ciliated epithelium.

CYSTS OF KOBELT

These are thin-walled, pedunculated cysts about the size of a pea (Fig. 393). They are frequently met with, and are seated at the side

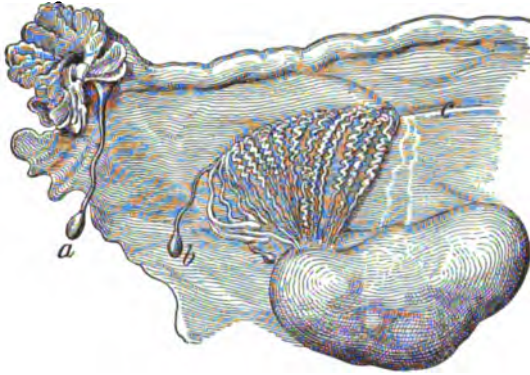


Fig. 393.—Fallopian tube, ovary, and parovarium: *a*, Hydatid of Morgagni; *b*, cyst of Kobelt's tube; *c*, Gärtner's duct (Penrose).

of the ovary. The wall is fibrous, the lining membrane composed of cubical epithelium, and the contents a clear serous liquid. The cyst results from distention of one of Kobelt's tubes in the parovarium.

THE FALLOPIAN TUBES

Development and Anatomy.—The tubes are formed from the upper ends of Müller's ducts. The lower ends of the ducts fuse to form the uterus and vagina. Each tube is covered by a peritoneal coat, and its walls consist mainly of longitudinal and circular muscle-fibers. The mucosa is thrown into well-marked longitudinal plications, which at the uterine end are further complicated by secondary elevations. The epithelial lining consists of columnar ciliated cells.

CONGENITAL ABNORMALITIES

The tubes may be absent or may be defective. Congenital atresia is occasionally observed. The tubes may be unusual in length and may communicate with the uterus in abnormal situations.

CHANGES OF POSITION

In dislocations of the ovaries the tubes are correspondingly dislocated. Independent of displacements of the ovary, the tubes may be distorted or pulled out of their usual position by inflammatory adhesions, and may thus be bent at sharp angles or bound down in various malpositions.

STENOSIS

Congenital stenosis of the tubes, or complete closure of the lumen, may affect the entire length of the tube or a limited portion, principally near the middle. Acquired stenosis may result from pre-existing disease of the tube itself, or from adhesions secondary to localized peritonitis. The most frequent situation in these instances is the abdominal or fimbriated end. A narrowing of the lumen of the tube may be occasioned by angulation or by dislocations.

DILATATION

Dilatation on the proximal side of obstructions or stenosis is frequent. The dilatation is more marked when inflammatory conditions of the mucous membrane are present. The abdominal end of the tube may enlarge so as to form a cyst of considerable size, filled with serous or seromucous liquid, when the middle portion is stenotic. When the lower end is obstructed the entire tube becomes dilated, and it frequently shows a tortuous and irregularly pouched condition, due to its attachments to the broad ligament. In such instances the mucous membrane is pushed inward at the bends, and projects prominently into the lumen of the tube. Secondary changes of the epithelial lining are not unusual in consequence of the irritation of the retained secretions. The normal epithelium may be wholly lost and the lining may consist of squamous epithelial cells. Purely inflammatory dilatations will be referred to below.

CIRCULATORY DISTURBANCES

Active hyperemia of the mucous membrane may be a part of acute inflammation of the tubes, and is very frequently found at the fimbriated extremity in association with peritonitis. The mucous membrane is swollen and bright red in color. There may be excess of mucous secretion.

Passive hyperemia occurs in conditions in which the general venous circulation in the abdomen is impeded.

Hemorrhages into the tubes may occur physiologically during the menstrual period, and sometimes considerable amounts of blood are found under these circumstances. Small hemorrhages into the mucous membrane may occur in association with inflammations of the tubes and in the course of some of the infectious diseases.

Hematoma of the tube, or the collection of blood in the tube, results from stenosis of the uterine end with accumulation of the menstrual discharges in the outer portions. The blood may remain in a more or less natural condition for a long time, or may undergo secondary changes. Sometimes it discharges through the abdominal end of the tube into the peritoneal cavity and leads to retro-uterine hemocele.

INFLAMMATIONS

Inflammation of the tubes, or salpingitis, may be acute or chronic.

Acute salpingitis presents itself in several forms, such as an acute catarrhal and a suppurative form. In most cases the inflammation results from the entrance of irritants from the uterus, and the tubal disease is secondary, therefore, to endometritis or to other disease of the uterus. Among the micro-organisms discovered, streptococci, staphylococci, the *Diplococcus pneumoniae*, and the *Bacillus coli communis* may



Fig. 394.—Acute septic salpingitis: section about the middle of the tube (Beyea).

be mentioned, but the gonococcus is by all means the most frequent in the non-puerperal cases. The infective organisms may extend directly along the mucous membrane or, more rarely, may reach the tubes through the lymphatics. In rare instances salpingitis may be secondary to local peritonitis.

Pathological Anatomy.—In acute catarrhal salpingitis the mucous

membrane is swollen, hyperemic, infiltrated with round cells, and covered with more or less abundant mucous secretion, which may distend the tube considerably. In the later stages the secretion is apt to become mucopurulent. Interstitial inflammation, with thickening of all of the layers of the tube wall, is frequently a secondary result. In acute suppurative salpingitis the walls of the tube are infiltrated with round cells (Fig. 394), the mucous surface discharges abundant pus, and the tubes may become distended with this exudate if the abdominal and uterine ends are closed by the inflammatory process. The mucous membrane in these cases is intensely inflamed and often slightly ulcerated upon the surface. Sometimes the distention is so great that the tubes are converted into pus-sacs the size of an egg or a small lemon. In case of acute suppurative or necrotic salpingitis secondary to puerperal sepsis the mucous membrane may be covered with a necrotic membrane; the term *diphtheritic salpingitis* has sometimes been applied to such a condition.

The exudates within the tube may remain for a long time without change, or may undergo gradual inspissation, and sometimes even

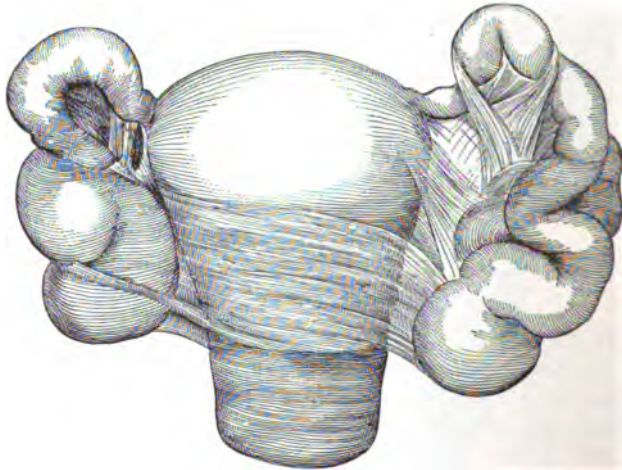


Fig. 395.—Chronic salpingitis: both Fallopian tubes are closed and adherent (Penrose).

calcification occurs. When ulcers of the mucous membranes have formed, rupture of the tube and consecutive peritonitis may occur, especially during straining efforts, as in labor. Acute local or general peritonitis more frequently results from discharge of infective matter from the abdominal end of the tube. Localized peritonitis is very common in acute cases, but the tube rarely ruptures under ordinary circumstances. It seems very distensible and localizing adhesions soon form, as in the case of any peritoneal congestion.

Microscopically, in all forms of salpingitis extensive round-cell infiltration is observed in all of the layers of the tubes. Plasma cells are especially prominent.

Chronic salpingitis, as a rule, results from the continuation of an acute form. The wall of the tube becomes thickened and the muscular layer is often hyperplastic. Proliferative changes in the mucous membrane are not unusual and may lead to actual polypoid outgrowths. Occasionally small follicular formations are seen in the mucosa, but ulcerations of the mucous membrane are infrequent. When the inflammation extends to the serous coat, inflammatory adhesions are frequently formed (Fig. 395), and may bind the tube firmly to adjacent parts and occasion great congestion or distortion. Very often the abdominal end of the tube becomes occluded by inflammatory adhesions or by inversion and agglutination of the fimbriæ. At the same time the swelling of the mucosa obstructs the uterine end, and in consequence the tube becomes a closed pouch which fills with pus (*pyosalpinx*), sero-purulent liquid (*hydrosalpinx*, Fig. 396), or hemorrhagic fluid (*hemato-*



Fig. 396.—Hydrosalpinx, showing complete inversion of the fimbriæ (Penrose).

salpinx). Intercurrent acute salpingitis frequently takes place in cases of chronic tubal disease.

INFECTIOUS DISEASES

Tuberculosis of the tubes may be either primary or secondary, and is probably much more frequent than has been supposed. Secondary tuberculosis may occur in the miliary form in association with tuberculosis of the peritoneum, other parts of the genitalia, or with general tuberculosis. In other cases secondary tuberculosis leads to caseous and fibrous changes in the walls of the tubes. The latter become greatly thickened, and, microscopically, there is found a diffuse cellular infiltration with scattered giant cells and here and there definite tubercles. The fibrous changes progress more slowly, and may eventually become the conspicuous feature. Primary tuberculous salpingitis is similar in its appearance to the form just described. The infection may occur through entrance of the organisms at the uterine end of the tube, and certain observations would indicate that pre-existing gonorrheal salpingitis predisposes to secondary tuberculous infection. There are

usually inflammatory adhesions of the tubes to the neighboring organs, and particularly to the ovary, and secondary miliary tuberculosis of the peritoneum is frequently observed (Fig. 397). The lumen of the tube is filled with purulent liquid, and sometimes certain portions, particularly the abdominal end, may be greatly distended, forming cysts containing puriform liquid.

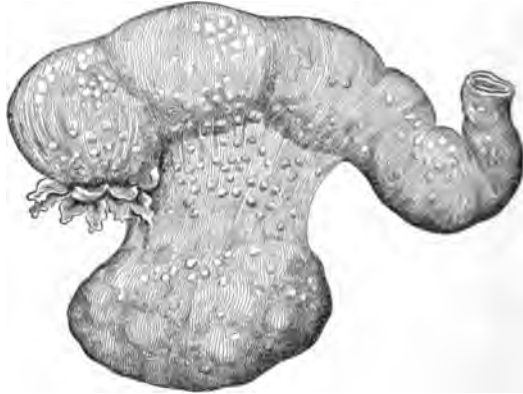


Fig. 397.—Tuberculosis of the Fallopian tubes. The disease has extended to the peritoneum, which is covered with tubercles (Penrose).

Syphilis has been observed in the form of gummata, and also in the form of diffuse sclerosis, in cases of congenital origin.

TUMORS

Fibromata and **fibromyomata** are met with in the external walls of the tubes as nodular masses. They frequently undergo secondary calcification. **Lipoma** occurs in the external coat lying between the layers of the broad ligament.

Papillomatous elevations of the mucous membrane are quite frequent, and in some cases a transformation of papilloma to carcinoma takes place. Probably most instances of **primary carcinoma** of the Fallopian tubes have this origin. **Secondary carcinoma** may result from extension of uterine cancer.

Sarcoma occurs in various forms, and **syncytioma malignum** may affect the tubes after tubal pregnancy.

Cysts of the tubes are usually the result of localized distentions of the lumen in consequence of obstructions. Small cystic formations of obscure origin are sometimes found in the peritoneal covering of the tubes and along the attachment of the broad ligament. Their contents may be colloid or serous.

The *hydatids of Morgagni* are small cystic formations about the size of a pea, hanging by a long pedicle at the fimbriated end of the tube. They are probably the result of distention of the closed end of Müller's canal.

Tubo-ovarian cysts are formed by distention of the abdominal end

of the tubes when the fimbriated extremities are attached to the ovary, or in other cases may be the result of rupture of follicular cysts of the ovaries themselves into the abdominal end of the tubes.

PARAMETRIUM

The tissues below the tubes and ovaries at the sides of the uterus are known as the *parametrium*, a highly vascular area containing the draining elements of the pelvis. It is of great pathological importance in the various inflammatory lesions emanating from the lower uterine segment. As infection spreads from this region the parametrium reacts promptly with serous, then cellular, exudate, and an acute inflammatory mass arises. While it is, in a sense, a local peritonitis, the possibility of infective thrombosis of the large veins render spread of infection easy, and the chronic adhesions remaining after recovery lead to uterine displacements and fixative adhesions. Abscesses may spread to Douglas' pouch. Hemorrhages from the large vessels in the parametrium may spread into this pouch or between the layers of the broad ligament.

EXTRA-UTERINE PREGNANCY

Etiology.—Any obstruction to the downward migration of the ovum may lead to its retention and development in abnormal situations. The actual case is usually difficult to determine. Impregnation possibly frequently takes place in the Fallopian tube; but unless some obstruction arrests the passage of the ovum into the uterus, normal uterine gestation takes place. Swelling or rapid decidua formation of the mucosa of the tubes may be one of the causes, and chronic salpingitis, by causing destruction of the cilia of the epithelial cells and thickening and adhesions of the walls of the tubes, acts in a similar manner. Any other form of obstruction, as by tumors or external compression, may be included among the etiological factors; a condition of some importance in the causation of ectopic pregnancy is the presence of diverticula of the tube near the uterus where an impregnated ovum may lodge.

Varieties and Pathological Anatomy.—All cases of extra-uterine pregnancy are probably in the beginning tubal pregnancies. This condition may occur in any part of the tube. It is rarely found at the uterine end, but may occur there in that part of the tube which is embedded in the wall of the uterus. The term *interstitial pregnancy* is applied to this form.

Tubal Pregnancy.—The changes which occur in the tube are analogous to those met with in the uterus. The same forms of membranes and deciduæ are developed, and a placenta develops as in the uterus. The muscularis of the tube may hypertrophy somewhat, but in the end the increasing size of the contained ovum leads to thinning and stretching of the walls of the tube. It is an interesting fact that the mucous membrane of the uterus forms a decidua of more or less complete development in cases of extra-uterine pregnancy (Fig. 398).

Among the terminations of tubal pregnancy are the following:

1. The tube may rupture into the broad ligament, into the peritoneal cavity, or, in cases of interstitial pregnancy, into the uterus. As a result of these accidents hematoma of the broad ligament, hematocele, and local or general peritonitis may occur, or sudden death may take place as a direct result of the hemorrhage. Sudden death from collapse is more frequently due to this cause than has generally been supposed.

2. The ovum may be destroyed in the tube and the gestation cease. In this case the fetus subsequently undergoes various changes. More or less degeneration usually occurs, and shapeless masses or adipocere may result. In other cases calcification of the remnants of the disorganized fetus leads to the formation of a *lithopedion*. This may take place within the tube, or after rupture of the tube and enclosure of the fetus in a sac formed by circumscribing peritonitis.

3. Premature discharge of the ovum (*tubal abortion*) may occur, and the gestation may terminate without serious results. In other cases, however, it leads to a discharge of the blood through the unclosed

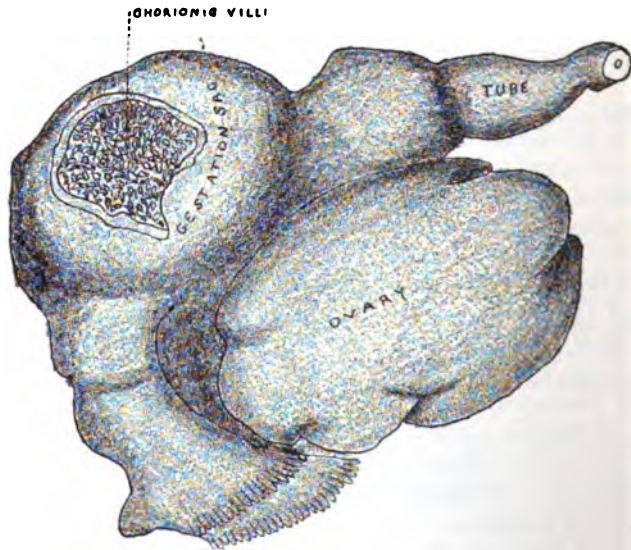


Fig. 398.—Tubal pregnancy, removed before rupture. The opening that has been cut in the tube shows the chorionic villi (Penrose).

abdominal ostium of the tube into the peritoneal cavity; and hematocele, peritonitis, or sudden death from hemorrhage may occur.

4. In very exceptional cases tubal pregnancy goes on to full term without rupture of the tube. Spurious labor may then come on, the fetus, as a rule, perishing. The liquor amnii is absorbed, and degenerative changes leading to mummification, or the formation of adipocere or of a lithopedion, take place. The mummified fetus may remain for many years. Very rarely after spurious labor the fetus is discharged into the peritoneal cavity, and may be delivered through the rectum or in other ways.

Abdominal Pregnancy.—This term is given to cases in which the tube has ruptured and the ovum, enclosed in its membranes, escapes into some part of the abdominal cavity, where it remains free or surrounded by adhesions the result of peritonitis. The placenta, as a rule, remains in the tube; but it may also establish secondary attachments to parts of the peritoneum. Primary abdominal pregnancy—that is, impregnation and gestation in the abdominal cavity—does not seem ever to occur.

THE VAGINA

PROLAPSE OF THE VAGINAL WALLS

Prolapse of the anterior or posterior wall of the vagina may be due to abnormal relaxation of the tissues, or it may be secondary to prolapse of the uterus and similar conditions that press the vaginal walls downward. Not infrequently the posterior wall of the bladder is dragged downward with the anterior wall of the vagina, and *vaginal cystocele* results. Similarly, the anterior wall of the rectum may be carried downward with the posterior wall of the vagina; this is termed *vaginal rectocele*.

STENOSIS OF THE VAGINA

Congenital stenosis is rare. More frequently the lumen of the vagina is narrowed by contraction of cicatricial tissues formed in inflammatory diseases of the walls, or by adhesion of the opposite surfaces following ulcerations. Complete occlusion may occur in the latter form of cases, especially in old women. Atresia leads to obstruction of the discharges from above, and when menstruation is due causes collection of blood in the vagina (*hematocolpos*) and in the uterus (*hematometra*).

WOUNDS AND FISTULÆ

Injuries to the vaginal walls may be caused by the insertion of sharp bodies or instruments, or by coitus. Much more frequently injuries are due to stretching or pressure during labor. Superficial lacerations caused by overdistention are frequent, but more extensive injuries may be caused by prolonged pressure of the infant's head or by instruments used in delivery. In such cases infection and phlegmonous inflammation are prone to occur, and vesicovaginal, urethrovaginal, or rectovaginal fistulæ are sometimes the result. The urine or feces may be discharged through the vagina, and often cause secondary inflammations of the entire vaginal mucosa.

Similar fistulæ may be due to ulcerative processes of other kinds, to necrosis of carcinomata of the vagina, or to diseases of the bladder or rectum.

CIRCULATORY DISTURBANCES

Active hyperemia occurs in the early stages of inflammation. The mucous membrane is light red in color and a little swollen.

Passive hyperemia is frequent in pregnancy, and occurs in consequence of pressure due to other causes, such as uterine tumors and the like. The mucosa becomes swollen and edematous, and may be moist from increased secretions.

Hemorrhages into the vaginal walls are most frequently due to traumatism. Inflammation and ulceration may result from the hemorrhagic extravasation.

INFLAMMATIONS

Acute Catarrhal Inflammation, Vaginitis, or Colpitis.—This condition is frequently due to gonorrheal infection, but may result from other causes, such as mechanical and chemical irritants, or in young girls from the invasion of the *Oxyuris vermicularis* from the rectum. The mucous membrane is usually deeply congested, and the surface is covered with mucopurulent exudate. In gonorrheal cases the cervix uteri and urethra are, as a rule, coincidentally affected.

Exfoliative Vaginitis.—In rare cases of intense catarrhal vaginitis, in which the deeper layers of the mucosa are principally involved, membranous formations, consisting of parts of the superficial epithelial layers, may be discharged.

Pseudomembranous vaginitis may occur in association with various infectious diseases, such as pneumonia, pyemia, cholera, etc.; but it is more frequently the result of pressure-necrosis and infection occurring during labor, and is one of the lesions of puerperal sepsis. The surface of the vagina is more or less extensively covered with a dirty and exfoliating pseudomembrane. After discharge of the latter ulcerations are often formed. Extensive necrosis of the vaginal walls may occasion great destruction, and in some instances phlegmonous inflammations of the perivaginal tissues may cause separation of the mucosa.

Other forms of vaginitis are *erysipeloid*, *aphthous*, and *emphysematous*. They are not peculiar in manifestation, but show the usual characters of these infections. The identity of the last has been questioned. It is supposedly due to an anaërobic organism and is common after labor.

Chronic catarrhal vaginitis may be the continuation of an acute inflammation, or may occur in a gradual manner in women reduced in vitality. The mucosa usually presents appearances somewhat like those of acute cases, though the congestion is less marked. Abundant mucopurulent or mucous discharge (leukorrhea) may be present. Erosions of superficial epithelium and enlargements of the lymphoid follicles are sometimes observed. In long-standing cases the surfaces may be smooth and the entire mucosa somewhat indurated (*senile vaginitis*).

Kraurosis vulvæ is a hyperplastic condition of the deep connective tissue which causes atrophy of the mucosa and submucosa of the

vagina, labiæ, and adjacent parts of the vulva. The mucosa of the affected areas is dry, glistening and hard, often fissured, and contractions of the vaginal outlet are common. The color of the surface is grayish or dark red. The etiology is obscure.

Elephantiasis of the labiæ or clitoris may be congenital, or may result from local inflammatory conditions or obstructions of the lymph-channels. The affected parts are sometimes enormously enlarged. The surface is smooth or nodular and is gelatinous or hard in consistency. As elsewhere, the histology is that of a fibrous overgrowth with lymphæctasia.

INFECTIOUS DISEASES

Tuberculosis may occur in the form of ulcers associated with uterine tuberculosis, or in the form of lupus from extension of the latter from the vulva.

Syphilis.—Chancres, mucous patches, and simple inflammation may occur in any part of the vagina, and circumscribed (gummatous) or diffuse infiltrations have been described.

TUMORS

Fibroma and **myofibroma** may arise in the muscular layer of the vaginal wall, and may project as nodular masses or assume a polypoid form.

Sarcoma may occur as a circumscribed mass, but more commonly as diffuse infiltration or grape-like masses, which tend to ulcerate.

Papillomata are not infrequent, in the form of small warts or as considerably elevated condylomata.

Carcinoma of the vagina is most frequently secondary to cervical cancer. Similarly, it may follow cancer of the vulva. Primary carcinoma of the vagina is rare. It occurs in the form of a circumscribed villous projection.

Cysts of the vaginal walls vary in size and number. Frequently they are multiple, and the size ranges from scarcely discoverable cavities to those the size of an egg. The contents are usually serous and colorless, or, less frequently, of brownish color. In some instances a flat epithelial lining has been discovered. The origin of these cysts is probably variable. Some seem to arise from remnants of the lower end of the Wolffian duct; others are probably lymphangiectatic. The multiple small cysts sometimes occurring in pregnancy are due to follicular distentions, or to small hemorrhages with subsequent cystic change.

THE VULVA

The most common anomalies of the vaginal entrance take the form of hypertrophy, particularly of the clitoris, but also of the labia, of hypoplasia combined with imperfect development higher in the genitalia, of reduplication or fusion of the labia, and of imperforate hymen,

or one with several openings. Hernia may occur into a patent canal of Nuck in the labia majora.

WOUNDS

Injuries of the vulva frequently occur during labor. Laceration of the fourchette is very common, and in a considerable proportion of cases more extensive tears extending into the perineal body, and sometimes through this into the rectum, are observed. Prolonged pressure and contusion during labor may occasion hemorrhages into the tissues of the vulva.

CIRCULATORY DISTURBANCES

Active hyperemia is met with in acute inflammations.

Passive hyperemia and **edema** occur in conditions in which there is general venous stasis, as in cardiac or pulmonary disease. They are also met with in pregnancy. The vulva is dark red in color, sometimes cyanotic; the subcutaneous and submucous tissues become edematous, and in consequence the labia majora may swell enormously.

Hematoma of the vulva is caused by compression and contusion of the vulva during parturition, or less frequently at other times. Varicosity of the veins is a predisposing cause of importance. Considerable masses of blood ("thrombi") accumulate in the submucous tissues of the vulva and vagina. These may be subsequently absorbed, or they may discharge through the skin in consequence of superficial ulcerations and ruptures. Infection of the thrombus may cause abscess of the labia or other affected parts.

INFLAMMATION

Acute catarrhal inflammation results from the same causes as occasion acute vaginitis. The pathological appearances are, in general, the same, though edematous swelling is likely to be more marked. Distention of the glands of Bartholin and secondary abscess-formation in these glands are common conditions in gonorrheal vulvitis. Vulvitis may be of erysipelatous form, upon which gangrene may supervene. Noma has been observed on the external female genitalia.

Epidemic vulvovaginitis of children, in all probability due to the gonococcus, appears frequently in hospitals and other institutions. The origin and method of spread are often obscure, and the disease is very difficult to eradicate. The symptoms and signs may intermit, but in their absence the person remains infective.

Chronic inflammation sometimes follows acute vulvitis. Considerable hyperplasia of the mucosa is sometimes the result. Erosions and ulcerations are less frequent.

Phlegmonous inflammation, or abscess, of the submucous tissue of the labia majora sometimes results from extension of a similar process in the adjacent parts, or may be the direct result of injuries and hematoma, with secondary infection.

INFECTIOUS DISEASES

Diphtheria sometimes attacks the vulva, especially in puerperal women. The pathological conditions are similar to those observed in other mucous membranes.

Tuberculosis may occur in the form of lupus. The lesions are irregular ulcers with elevated edges and more or less necrotic bases.

Syphilis.—Chancres and mucous patches are met with on the sides of the labia and elsewhere. Condyloma acuminatum, or venereal wart, is frequently seen upon the vulvar surfaces. Histological study shows it to be a hypertrophy of the dermal papillæ with hyperplasia of all layers of the epiderm.

Chancroids occur in the same situations as chancres. Very often opposite sides of the vulva are involved by attrition.

Gangrene of the vulva may be the consequence of severe contusions or inflammations occurring in the course of various infectious diseases.

TUMORS

Fibroma, fibromyxoma, and myofibroma are occasionally met with as nodular tumors or polyps arising from the labia majora. **Lipoma** and **sarcoma** may present a similar macroscopical appearance. All of these growths are rare.

Elephantiasis vulvæ is a not infrequent affection, especially in eastern and tropical countries. It may be due to congenital dilatations of the lymphatic channels, or to lymphangiomatous tumor-growths. More frequently elephantiasis is caused by filariæ and inflammatory conditions that occasion obstruction to the flow of the lymph. In some instances the etiology is very obscure.

Pathologically, elephantiasis consists of a thickening of the subcutaneous connective tissue, with more or less involvement of the skin as well. The disease may begin in the clitoris, or in one or other of the labia, and may be confined to the part primarily affected, or may extend to other parts. The affected portions are tough and edematous; the skin is tightly bound to the subcutaneous tissue. The surface may show dermatitis, but in some cases is smooth. Superficial ulcers may occur, and sometimes the dilated lymph-channels communicate with the surface, discharging lymph (lymphorrhæa).

Papillomatous tumors are not infrequent in syphilitic women in the form of elevated condylomata. A somewhat analogous condition of obscure etiology is that termed *caruncle*. It presents itself as a papillomatous and highly vascular elevation at the meatus of the urethra.

Adenoma arising from the glands of Bartholin has been described.

Carcinoma is uncommon. It most frequently arises from the clitoris, but may affect any portion. Glandular cancer may begin in Bartholin's glands.

Cysts are quite frequent. Small retention-cysts, containing pul-

taceous (atheromatous) matter, are sometimes met with in the labia majora, and in the great majority of cases are retention-cysts of the glands of Bartholin. Larger cysts, containing serous or somewhat blood-stained liquid, may result from hematomata, or may be lymphangiomatous in origin. Hydrocele of the canal of Nuck has the superficial appearances of a cyst of the labia.

THE DECIDUA, PLACENTA, AND FETAL MEMBRANES

Anatomical Considerations.—The fetus is enclosed within a delicate fibrous membrane, the *amnion*, and this is covered with a second membrane, the *chorion*. After the deposit of the ovum in the uterus the mucous membrane of the latter undergoes a form of hyperplasia, in which the uterine glands and the blood-vessels take part conspicuously, and thus the organ becomes lined with a thickened mucosa. The latter is termed the *decidua vera*. A reflection from this covers the fetus enclosed in its membranes, the reflection being known as the *decidua reflexa*. At about the fifth month of development the decidua reflexa and the decidua vera unite and fuse. The portion of the decidua vera at which the placenta is subsequently located is termed the *decidua serotina*. In this portion the vascular system is particularly marked, and is composed of large venous sinuses with thin walls. The fetal chorion carries on its outer surface numerous small projections, or villi. In the region of the decidua serotina these villi undergo marked hyperplasia and bury themselves between the venous sinuses of the decidua. At the junction of the villi and the decidua two layers of cells are developed. The first, immediately covering the villi, consists of cubical epithelial cells (Langhan's cells). Outside of these, and uniting the villi with the maternal tissue, is a layer of clear protoplasmic material containing large nuclei. This has the appearance of nucleated protoplasm, rather than that of collections of cells of definite outline. This protoplasmic layer, *syncytium*, is probably, like Langhans' cells, derived from the covering of the chorionic villi, though some authorities contend that it is maternal in origin.

ABNORMALITIES OF DEVELOPMENT

The Placenta.—Abnormal smallness of the placenta, or hypoplasia, and abnormal largeness are occasionally observed. More frequently an adventitious placenta (*placenta succenturiata*) may be attached to the main placenta or may lie near it. Abnormal location of the placenta at or near the neck of the uterus (*placenta prævia*) is an important condition, from its liability to cause hemorrhage and miscarriage.

The Umbilical Cord.—Occasionally the cord is divided near its placental end into two or more branches. The placenta may be correspondingly divided or single. The attachment to the placenta may be marginal instead of central, and sometimes the blood-vessels spread out into a broad marginal attachment, with absence of their gelatinous covering. The latter is termed *velamentous insertion*.

Abnormalities of the blood-vessels, such as branching, a single artery, two veins, etc., are unimportant.

Twists and knots of the cord are frequent, and may strangle the cord and stop the circulation, causing death of the fetus.

Thickening of the intima of the umbilical vein and of the adventitia of the arteries is probably syphilitic in nature.

CIRCULATORY DISTURBANCES

Hydrorrhœa gravidarum is a condition in which abundant serous or somewhat turbid liquid is secreted from the deciduæ. The condition occurs in women suffering from general anemia, but is probably due to local conditions within the uterus. Abortion or miscarriage is not unusual.

Hemorrhages from the decidua or into the decidua and placenta are not infrequent. Hemorrhages from the surface may be due to preceding decidual disease, or may be obscure in origin. Large hemorrhages may cause rapid discharge of the uterine contents. In cases of that abnormal position of the placenta called placenta prævia hemorrhages are frequent.

Fleshy moles or polypi are the terms used to designate formations in the deciduæ and placenta resulting from gradual hemorrhage and destruction of the ovum. The hemorrhage takes place in the decidua, and then extends between the chorionic villi into the fetal membranes, which may be more or less extensively torn apart. Irregular masses of clotted blood attached to the placental site and to the chorion are discovered. The amniotic cavity contains viscid fluid and the ovum is more or less completely disorganized. Sometimes no recognizable remnants can be found. The moles may be retained a long time and may undergo secondary calcareous infiltration. Usually they are soon discharged.

Placental Infarcts.—This term is applied to light-colored, more or less indurated areas met with in the placenta, deciduæ, and sometimes in the chorion. The nature of these formations is still somewhat uncertain. They are composed of fibrin of reticulated or granular character, with occasional areas of softening and hemorrhagic accumulations, and are not rarely surrounded by a zone of cellular infiltration. Some of these "white infarcts" may be only an exaggeration of the normal coagulation necrosis occurring toward the end of pregnancy. Some are surely due to hemorrhages. When they are extensive it is very probable that they represent results of disturbances of circulation caused by thickening of the walls of the blood-vessels.

INFLAMMATION

Inflammations of the placenta (*placentitis*), of the chorion villi, or of the decidua (*endometritis decidualis*) may occur in association with preceding diseases of the uterus, and especially in cases of syphilis of the mother or fetus. The inflammation takes the form of cellular in-

filtration and induration. This may begin in the decidua and extend to the placenta, and may be of a diffuse or circumscribed character. The villi of the placenta may be greatly compressed by the inflammatory tissue, and may suffer fatty degeneration and atrophy. In other cases the inflammatory changes are most pronounced in the walls of the blood-vessels and around the vessels of the chorion and umbilical cord. Nodular thickening or diffuse induration results, the latter especially in cases in which coincident involvement of the chorionic villi has occurred.

Diffuse hyperplasia of the decidua is sometimes described as *endometritis decidualis*. The inflammatory nature of such cases, however, is uncertain.

INFECTIOUS DISEASES

Tuberculosis of the placenta was suspected as a possible condition long before positive demonstrations were made. In recent years, however, a number of undoubted cases have been described. Macroscopically, there may be but little change in the appearance of the affected parts.

Small tubercles, containing giant cells and tubercle bacilli, first appear in the decidua serotina, and later invade the placental and chorionic tissues between the villi. The epithelial covering of the villi undergoes hyperplasia, forming collections of large cells. Warthin says that the decidual cells do not form tubercles, the tubercle bacillus being primarily necrotizing to the placental cells, but that the fixed tissue elements in the neighborhood supply cells for the tubercle. In the later stages of the process caseous necrosis of the tuberculous structures takes place, and the villi themselves suffer invasion and degeneration. Their blood-vessels are frequently occluded by hyaline thrombosis and proliferation of the endothelial lining. Tubercle bacilli have been demonstrated in the vessels of the fetal side of the placenta, though less frequently and abundantly than in the maternal vessels.

Syphilis of the placenta may take the form of a diffuse hyperplasia, or of a nodular or gummatous process. The placenta is enlarged, indurated, and heavy; it is light colored, in localized areas or diffusely. Microscopically, cellular proliferation springing from the adventitia of the blood-vessels is the characteristic feature. The epithelial cells covering the villi may proliferate, and fatty degeneration of the body of the villi is not infrequent. The chorion and amnion may be diffusely thickened. The syphilitic nature of cases conforming with the above description is often doubtful, as is also the nature of some of the cases of placentitis that are often described as syphilitic.

HYPERPLASIA

Occasionally, diffuse or circumscribed thickening of the decidua occurs in association with chronic metritis; the term *endometritis decidualis* is applied to this condition. (See Inflammation.)

Placental Polypi.—Portions of the decidua, and especially the placenta, retained in the uterus, may remain firmly attached and may undergo subsequent proliferative change, forming polypoid tumors of adenomatoid structure. These are particularly frequent after abortion.

Destructive Placental Polyps.—Like the preceding, these originate in retained portions of the placenta, but differ in the more active proliferative changes that take place. On the uterine surface they are covered with fibrin and blood-clots, and at their attachments are composed of variously formed cells, including large epithelium-like cells enclosed in a vascular stroma. The growth may involve the uterine tissues to a considerable extent. Its nature is obscure in some particulars, but resembles that of the syncytioma.

Hydatid moles present themselves as rounded, rather translucent bodies hanging by their pedicles to the outer surface of the chorion, and often attached one to another in clusters, resembling a



Fig. 399.—Section of a hydatid mole.

bunch of grapes. Microscopically, they are found to be composed of myxomatous or more or less edematous fibrous tissue containing few cells and free nuclei, and covered on the outer surface by epithelial cells (Fig. 399). The nature of the hydatid mole has been the subject of some controversy. Virchow taught that they are simply myxomatous hypertrophied chorionic villi. More recent investigators have found evidences of active hyperplasia of the superficial epithelium of the chorion villi, with secondary degeneration, edema, and necrosis. This accounts for the fact that sometimes the moles extend deeply into the decidua, and even into or through the muscular wall of the uterus.

Hydatid moles are especially met with in women suffering from chronic constitutional diseases (nephritis, anemia) and in those becom-

ing pregnant late in life. Endometritis seems to bear some relation, though the disease is evidently one of the fetal rather than maternal tissues. This is shown by the limited extent of the disease in some cases, and by the fact that in twin pregnancy the membranes of only one of the fetuses may be affected. When the disease is extensive death of the fetus usually results, and the moles are discharged in the form above described, or enclosed in clotted blood.

Syncytioma Malignum.—The nature and peculiarities of this condition have been sufficiently described (see page 258).

THE PENIS AND SCROTUM

CONGENITAL ABNORMALITIES

Absence of the penis is rarely observed; more frequently it is abnormally small, resembling the clitoris of the female. Occasionally the organ is doubled, each half containing a duct, one for the discharge of urine, the other for seminal fluid.

Hypospadias is the condition in which the urethra terminates in an orifice on the under surface of the penis, in the pendulous portion or at the bulb, or occasionally at the root of the scrotum or in the perineum. With hypospadias there is usually some deformity of the scrotum, the commonest being a division into lateral halves containing the testes, or the latter may be in the inguinal canal or abdomen. *Epi-spadias* is a less frequent condition; the urethral orifice in this case is found upon the dorsal side of the organ. Excessive length of the prepuce is a frequent abnormality; there may be associated with this stenosis of the preputial opening, so that the glans penis cannot be exposed (*phimosis*).

The condition of *hermaphroditism*, or the presence of the genital organs of both sexes in one individual, is rare, while *pseudohermaphroditism* is more common. In the latter the genitalia are distinctly of one sex, although anomalous in formation, while the secondary sexual characters are those of the other sex.

INFLAMMATION

Inflammation of the mucous membrane of the glans penis (*balanitis*) or of the prepuce (*posthitis*) is not infrequent. Among the more frequent causes are uncleanness, with decomposition of smegma retained beneath the prepuce, irritation by the urine in cystitis or other inflammatory diseases, gonorrheal infection, and chancroids. The mucous membrane becomes swollen and red, and considerable purulent exudate may be discharged. Edematous swelling of the prepuce is frequent, and may cause inability to retract the prepuce over the glans (*phimosis*). In other cases the prepuce, previously drawn back, becomes so tensely swollen that it cannot be pushed forward to its normal position (*paraphimosis*).

In catarrhal inflammation of the prepuce there may be associated retention-cysts of the mucous glands. The cysts may rupture, causing small ulcerations. The inflammation may take a membranous or phlegmonous form; these may lead to phagogenic ulceration or gangrene and may extend to the body of the organ.

Inflammation of the cavernous bodies may result from traumatism, or from extension of gonorrheal urethritis, and may sometimes occur in infectious diseases, such as small-pox, pyemia, etc. The penis swells considerably, and abscesses or diffuse purulent infiltration may result. In traumatic cases with hemorrhagic exudation necrosis or gangrene may result. In case of favorable termination after severe inflammations deforming cicatrization may occur.

INFECTIOUS DISEASES

Syphilitic chancres and **secondary lesions** and **soft chancre** or **chancroid** are frequently located upon the prepuce or its frenum, or upon the glans penis. (The lesions are described in Part I.)

Tuberculosis is a rare condition in this situation. It has been met with in the form of necrotic ulcerations. It is very likely that direct infection of the penis may occur during coitus with a woman who has genital tuberculosis. In children it has been attributed to the practice in certain rituals of smearing the wound of circumcision with saliva.

TUMORS

Papilloma, or **condyloma acuminatum**, is not infrequent on the glans penis and prepuce. Sometimes it has a distinctly inflammatory origin, occurring in association with gonorrhea, syphilis, or other forms of local irritation; in other cases it originates without discoverable cause. There are usually several or many warty elevations, and occasionally a mass of warts is aggregated in a cauliflower fashion. Microscopically, condylomata are composed of a stroma of vascular connective tissue covered with hyperplastic epithelium. The cauliflower-form may be distinguished from epithelioma by observing that the mucous membrane is not infiltrated and is movable upon the underlying tissues.

Carcinoma (epithelioma) of the penis may arise from the glans or from the prepuce. It may present itself as an infiltrating growth with a tendency to ulceration, or as a papillomatous, cauliflower-like growth. In the latter case the primary growth is either papillomatous, with secondary carcinomatous alteration, or carcinomatous, followed by papillomatous outgrowths. Considerable destruction of the glans penis may occur, and metastatic nodules are frequently formed in the inguinal glands.

Epithelioma of the scrotum is comparatively frequent in chimney-sweeps and paraffin-workers.

Elephantiasis of the scrotum is a common disease of the East. The scrotum may be enormously enlarged. Some cases are due to

filariasis; in other cases filariæ cannot be demonstrated. Somewhat similar thickening of the prepuce is a rare condition.

Cysts.—Small cysts, due to occlusion of the glands of the mucous membrane and of the skin, are occasionally met with under the prepuce and in the scrotum. Dermoid cysts of the scrotum are occasionally observed.

Lipomata, angiomata, and fibromata are rare forms of tumors of the penis.

Concretions beneath the prepuce result from phimosis with retention of the smegma. Sometimes they increase by constant additions until they reach considerable size (200 g.). In one case seen by one of us gouty tophi in the prepuce grew to the size of a small lemon.

INJURIES OF THE PENIS

Direct traumatism may occasion serious laceration of the corpora cavernosa, especially when the penis is erect at the time of injury. Considerable hemorrhagic extravasation may occur, and inflammation or even necrosis and gangrene may ensue. Fracture of the penis is a term applied to rupture of the fibrous capsule of the cavernous bodies. Both this and less extensive lacerations occasion great hemorrhagic swelling, with subsequent inflammation or necrosis. Injuries to the penis may cause rupture of the urethra, with extravasation of urine.

THE TESTICLES

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The testicles are composed of tubules lined with cells, spermatogonia, from which the spermatozoa are derived, and of certain interstitial cells (cells of Leydig) which form a somewhat distinct glandular system. The sharp distinction drawn between these two components of the testicle by some experimenters has not been fully established.

Aside from its relation to the reproductive function accomplished by the production of spermatozoa, the testicles, as the ovaries in the female, have an important bearing on growth and metabolism. Early castration leads to *eunuchism*, in which bodily growth, and especially fatty deposition, may be excessive, while infantile characteristics and the arrest of development of certain accessory organs of sex are marked. Sometimes tumors of the testicles have occasioned precocious development. These effects are attributed to removal or stimulation of the function of the interstitial cells rather than of the tubular cells. The adrenals, hypophysis, and pineal gland seem to exercise some influence upon the testicle.

CONGENITAL ABNORMALITIES

Absence of one or both testicles is a rare condition. More frequently the organ is *hypoplastic*, remaining undeveloped through life, the man being infantile or effeminate. *Polyorchism* occurs at times.

The most frequent congenital abnormality is *cryptorchismus*, a condition in which one or both testicles remain in the abdominal cavity, in the inguinal canal, or elsewhere in the tract through which normal descent occurs. The undescended testicle may descend at or before puberty, or may remain fixed in its abnormal position. In the latter case, especially if the testicle is in the inguinal canal, secondary inflammation or atrophy may occur. Slight defects in the development of the testicle are not infrequent, but are unimportant. The causes of cryptorchismus are numerous, the most common being arrest of development, antenatal peritonitis, and a disproportion between the size of the organ and of the inguinal canal.

ATROPHY AND HYPERTROPHY

Atrophy may follow any form of inflammation of the testicle or epididymis, such as those occurring after gonorrhea, mumps, and other infectious diseases or traumatism. In other instances pressure upon the organ, as in hydrocele, tumors, etc., is the cause of atrophy. Atrophy also may occur in cryptorchism or when, by stricture of the vasa or ejaculatory ducts, semen is retained in the testes. Any of the above conditions, operative in early life, may lead to aspermia and sterility. Hypoplasia may accompany deficient thyroid or pituitary function. The most frequent form of atrophy is that which occurs as a natural process of involution in old age (*senile atrophy*).

The testicle decreases in size, increases in consistency from overgrowth of connective tissue, and is usually more pigmented than in health. Microscopically, the seminal tubules are found to have undergone fatty degeneration and contain fatty debris and blood-corpuscles.

Hypertrophy of one testicle may occur as a compensatory process in cases of disease, atrophy, or removal of its fellow, and after disease of the adrenal cortex. Hypertrophy of this sort has been produced experimentally in animals. The seminal tubules increase in size, but are otherwise normal.

DEGENERATIONS

Fatty degeneration is frequently observed in testes subjected to pressure through tumors or other pathological conditions, and in cases of atrophy of the testicle from any cause. The epithelium of the tubules is attacked and may be completely destroyed, with production of fatty detritus.

Myxomatous degeneration occurs in various tumors of the testis and in gummata.

Calcification may affect old inflammatory deposits, especially those of the epididymis.

Caseation is a frequent condition in tuberculous and syphilitic lesions; and abscesses may undergo a process of inspissation, with formation of dry, caseous material.

CIRCULATORY DISTURBANCES

Active hyperemia of the testis, epididymis, and especially of the membranes, occurs in association with acute inflammations.

Passive hyperemia is caused by pressure upon the veins or disease of the veins (varicosity). The testis and epididymis become swollen from edema, and, if the hyperemia persists, fatty degeneration and atrophy may result. Serous effusion into the tunica vaginalis (*hydrocele*) may be purely dropsical, but is more frequently inflammatory (see page 820).

Embolism of the spermatic artery may occasion hemorrhagic infarction, followed by necrosis or gangrene of the testis. This sequence has been observed in a few cases, and has been proved experimentally. Sometimes gangrene seems to be caused by phlebitis of the pampiniform plexus.

INFLAMMATION

Inflammation may involve the testis (*orchitis*), the epididymis (*epididymitis*), or the tunica vaginalis (*vaginitis testis*).

Etiology.—Traumatism is a frequent factor in the etiology, and causes inflammation of the epididymis and membranes more frequently than of the testicle itself. Blows, bruises, and contusions are the usual conditions that cause this form of inflammation.

In another group of cases the irritants are micro-organisms conveyed through the blood. Thus in typhoid fever, tuberculosis, pneumonia, and various forms of septicopyemia the specific organisms have been discovered in the areas of inflammation. Similar inflammations occur in mumps, scarlet fever, and small-pox, and are doubtless caused in the same way, though the specific organisms are unknown. In these cases the testis is more frequently affected than the epididymis.

In a third group of cases infection occurs through the vas deferens, and the epididymis is affected first and often alone. The most frequent infectious agent in this group of cases is the gonococcus; but other micro-organisms may enter the vas deferens, reach the epididymis and cause inflammation, in other diseases of the bladder or urethra, or after operations upon these parts, such as crushing vesical calculi, cutting urethral strictures, and the like.

Pathological Anatomy.—Inflammations of the different parts may be separately considered.

In **acute orchitis** the testis is more or less edematous and swollen on account of inflammatory exudation. Microscopically, the striking feature is round-cell infiltration of the intertubular tissues. This may be diffuse and uniform, or may occur in circumscribed areas, the latter being especially common in the orchitis of variola and pyemia. The round cells may infiltrate the walls of the tubules, and may be discharged into the tubules in great numbers. At the same time the epithelial cells may suffer degeneration and desquamation. Intense

orchitis may lead to the formation of abscesses, single or multiple. These may subsequently undergo complete absorption, or may become inspissated and encapsulated, the contents of such a focus consisting of fatty detritus and cholesterin. In other cases the abscess may rupture externally, and occasionally granulations springing from the tunica albuginea or the testis may protrude through the opening. The term *benign fungus* is applied to this condition.

Chronic orchitis usually results from the acute form. The inflammatory changes of the intertubular tissues gradually lead to induration, and the testis becomes hard and contracted, the connective tissue and septa being increased in density, the tubules at the same time suffering degeneration and atrophy. In cases following acute suppurative orchitis the tissues surrounding the inspissated abscess become sclerotic, and the tubules are in large part or wholly destroyed. Small nodular areas are discovered in such cases, and on section these are found to consist of a dense wall of fibrous tissue enclosing thickened pus containing fatty detritus and cholesterin. The membranes surrounding the testis are usually thickened and united by adhesions.

Chronic orchitis without a definite antecedent acute stage is a frequent result of syphilis (see page 821).

Acute epididymitis occurs when infective agents have reached the epididymis through the vas deferens. There is tense swelling of the epididymis, and not rarely associated inflammation with serous exudation in the tunica vaginalis. The testis is not, as a rule, involved. The process begins as an acute catarrhal inflammation of the tubules of the epididymis; later, cellular infiltration and occasionally abscess-formation occur in the intertubular connective tissues. The inflammation is sometimes completely resolved, but in other cases fibrous thickening, diffuse or nodular, results. Inspissated abscesses surrounded by fibrous tissue are sometimes seen, as in orchitis. The epithelium of the tubules embedded in the new-formed fibrous tissue may undergo a certain amount of proliferation, suggesting the appearance of adenoma or cancer. The vas deferens may be permanently obstructed, and the tubules on the proximal side and in the testis may undergo cystic distention. Extensive epididymitis very commonly causes atrophy of the testis.

Vaginitis testis and **periorchitis** are terms applied to inflammation of the tunica vaginalis testis. This condition is usually the result of orchitis or epididymitis, but may sometimes occur as a primary inflammation resulting from traumatism or other forms of irritation.

The tunica vaginalis is a reflection of the peritoneum, and inflammatory conditions arising in it resemble those of the abdominal peritoneum.

Serous or serofibrinous vaginitis testis is the most frequent form. This may be acute or chronic, and is characterized by the accumulation of small or large collections of serous liquid. In slowly developed cases, the quantity of liquid may be one or two liters. It may be clear serum, but often contains flakes of fibrin or leukocytes, and is sometimes

reddish from the presence of red blood-corpuscles. Sometimes the liquid is milky or turbid, and contains fat-droplets and cholesterin crystals. A chylous variety occurs in tropical countries, and is probably caused by the *Filaria sanguinis hominis*.

Hydrocele is the term used to designate effusions of these sorts. Sometimes the liquid contains spermatozoa, when the term *hydrocele spermatica* is applied. This condition is due to the escape of spermatozoa from improperly developed spermatic tubules or from ruptured cysts of the epididymis or testis. In certain cases it is difficult to distinguish hydrocele spermatica and spermatocele (see page 823).

When hydrocele persists the tunica vaginalis undergoes hyperplastic thickening, and small, wart-like elevations may be formed (*periorchitis prolifera*). These nodules may become separated and remain in the sac as free bodies, like those in the joints. Another result of the secondary inflammatory changes in the membrane is adhesion of the reflexions, causing a bilocular or multilocular hydrocele.

When the canal connecting the sac with the peritoneal cavity has remained patulous the fluid of hydrocele may be pressed into the abdominal cavity. The term *hydrocele processus vaginalis* is applied to such cases, and the term *hydrocele funiculi spermatici* to cases in which only the upper part of the vaginal canal is patulous and filled with liquid. *Hydrocele funiculi cystica* results from collections of fluid in the middle portion of the canal, the upper and lower ends being obliterated.

Purulent vaginitis testis occurs in association with epididymitis and orchitis, and sometimes primarily after traumatism. An ordinary hydrocele may be converted into a purulent collection by puncture with infected instruments. The sac is more or less distended with purulent liquid, and the surface of the membrane is covered with fibrinopurulent exudate. The pus may discharge externally, or may become inspissated; and extensive adhesions may obliterate the sac.

Hemorrhagic Vaginitis Testis.—In severe acute inflammations the exudation may be more or less hemorrhagic. More distinctly hemorrhagic forms of inflammation result from traumatism; in these cases there is first extravasation of blood and then inflammation. The sac may be lined with fibrinous and hemorrhagic deposits while the membrane itself is infiltrated and opaque. In the terminal stages considerable thickening and sometimes calcification of the tunica vaginalis are observed.

Inflammation of the vas deferens may be associated with epididymitis or orchitis, or may occur independently in cases of direct traumatism. In syphilitic disease of the testis, and less commonly in other forms of orchitis, the vas deferens may be greatly thickened.

Varicocele is a tumor made up of dilated vessels of the pampiniform plexus and spermatic veins. It is due to obstruction of the venous flow by foreign masses, or the cases arising without such reason are ascribed to the weight of the blood column upon vessels with poor walls and valves. It is commonest in the young, and appears most often on

the left side. The left spermatic vein empties at right angles into the renal vein, so that there is in this vessel a long column of blood in an almost directly vertical position.

INFECTIOUS DISEASES

Tuberculosis is most frequent in the epididymis, but may involve the testicle as well. The infection occurs in one of two ways: either through the vas deferens, in consequence of tuberculosis of the prostate, seminal vesicles, or bladder; or through the circulation in cases of pulmonary or other forms of tuberculosis. It has been shown that tubercle bacilli are discharged from the body in the seminal fluid in cases of pulmonary and other forms of tuberculosis; and when local conditions predispose tuberculous infection of the epididymis may occur. Gonorrheal epididymitis seems to constitute such a local predisposition. Primary hematogenous infection of the epididymis seems to occur in rare cases.

In cases of infection through the vas deferens there are formed in the walls of the tubule of the epididymis small tuberculous masses, which rapidly increase in size and run together, forming caseous areas of considerable size. Further invasion occurs along the lymphatic channels and the tubules, and rapid involvement of a considerable part of the epididymis results (Fig. 400). The tubule surrounded by tuberculous tissue may become filled with desquamated epithelium and puriform or caseous matter, and may be dilated in a cystic form. Extension to the testicle may occur, but is unusual.

Associated serous or serofibrinous vaginitis testis is not infrequent; and in some cases the tuberculous disease itself extends to the testicular envelopes and causes nodular elevations, or ulcerations and fistulous communications with the surface.

Hematogenous tuberculosis of the epididymis is, in the first place, of the miliary form, but the tubercles grow rapidly and caseous nodules are rapidly formed.

Tuberculosis of the vas deferens may be secondary to tuberculosis of the seminal vesicles and bladder, or of the epididymis. It is characterized by caseous swelling of the walls of the duct.

Syphilis is not infrequently seen in the testicle in the late stages of acquired syphilis and in congenital syphilis. The epididymis and the membranes are secondarily involved. Two forms may be distinguished. The more frequent is that in which diffuse induration of



Fig. 400.—Tuberculosis of the epididymis and testicle (modified from Bollinger).

the testicle occurs; in the less frequent variety there are circumscribed gummata. In the diffuse form the organ is more or less uniformly indurated, and on section dense bands of fibrous tissue are conspicuous. The tubules suffer compression, degeneration, and atrophy, and sometimes become converted into cheesy foci. The gummata have the usual translucent or cheesy appearance. When the membranes are involved diffuse thickening occurs; and in rare cases the disease extends to the skin, causing superficial granulations (*sypilitic fungus*). The vas deferens is often greatly thickened, as are also the walls of the blood-vessels of the testis and epididymis.

Lepra of the testis occasions nodular lesions and pressure-atrophy of the tubules. Lepra-cells containing bacilli, as well as free bacilli, occur in the tubules in abundance. This fact is important as indicating a possible mode of transmission of the disease.

TUMORS

Fibroma is occasionally observed in the rete testis and tunica albuginea as a small nodular tumor.

Chondroma is rare. It may occur in the epididymis or rete, as a single node or as multiple small nodules. **Osteoma** is very rare. **Myxoma** is rare, except in association with other tumors. **Rhabdomyoma** sometimes occurs in the form of flesh-like growths of the testis. None of the above occur frequently in pure form, being usually combined in various mixed tumors.

Sarcoma may occur in any of its various forms in the testis, and less commonly in the epididymis. The supporting tissue between the tubules is its usual starting place, but the "interstitial cells" are believed by some to be capable of sarcomatous growth. Sarcoma forms rapidly growing whitish or reddish tumors. Secondary changes, such as fatty degeneration, hemorrhage, cystic softening, and caseation, are not infrequent. Cystic dilatation of the seminal tubules may occasion marked changes in the appearance of the tumor. The cysts are small, and filled with turbid liquid containing fat, desquamated cells, and cholesterol; or large, and contain serous liquid, either clear, turbid, or blood-tinged. The lining epithelium of the cysts is columnar, or, in case of cysts of the epididymis, often ciliated. The walls of the tubules in some instances undergo active hyperplasia, giving rise to papillomatous elevations of the inner surface, and a truly adenomatous proliferation may occur. In the latter cases the tumor may be designated *adenosarcoma*. Growths of this variety are sometimes met with in young adults or children, and most frequently in the rete testis. They are more or less malignant, causing frequent metastasis along the lymphatics or blood-vessels. Sarcomatous change is not infrequently seen in congenitally misplaced testes.

Adenoma of the testicle is rare; much more frequently cystic tumors have a more or less adenomatous character (see Cysts).

Carcinoma usually appears in the testes and epididymis in a

medullary form, but occasionally a scirrhus growth occurs (Fig. 401). Mucoid and colloid degenerations are rather frequent, and cystic softening may occur. Cysts may also result from dilatation of the tubules. Cartilaginous areas are sometimes found in the stroma of the growth; to such the term *chondrocarcinoma* is applied. More or less complete destruction of the testicle and epididymis is frequent, but the tunica albuginea usually resists invasion for a considerable time. Carcinoma of the testicle seems to originate from the epithelium of the convoluted tubules. Metastasis through the lymphatics and blood-vessels is frequent, and extension through the testicular envelopes to the skin may occur; spread may follow the vas deferens to the retro-peritoneal tissues.

Teratomata and mixed tumors are common in the testicle. The most important of the former is the chorion epithelioma, while of the latter many combinations appear, cystic rhabdomyoma perhaps being the most frequent.

Cysts.—Retention-cysts of the tubules are frequent in cases of inflammation and induration of the testis and epididymis. Sometimes they contain a simple milky liquid; in other cases spermatozoa are found in the fluid, and to these cysts the term *spermatocele* is applied. The cysts may be numerous and small, or may be very large, containing a hundred or more cubic centimeters of liquid. The cysts are found in the body of the organ; but, when large, project from the surface. Very large cysts push the testicle and epididymis to one side. Occasionally, cysts originate from the hydatids or the paradidymis. These may be spermatoceles, when one of the vasa aberrantia opens into them.

Secondary proliferations of the epithelium of the cysts may convert a simple into a *papilliferous cystoma*; and occasionally the primary process seems to be one of adenomatous character, the cystic condition being the result of secondary distention or of the peculiar character of the acini formed.

Small cystic cavities may contain mucous liquid or thick, curdy material. In the latter case the term *atheromatous cyst* is applicable.

Dermoid cysts are occasional tumors of the testis proper. They may be simple sacs, lined with epidermal tissue and filled with pulta-



Fig. 401.—Carcinoma of the testicle (from a specimen in the Museum of the Philadelphia Hospital).

ceous matter; or *complicated dermoids*, containing teeth, bone, muscle-fibers, and nerve tissue.

PARASITES

Echinococcus cysts are encountered on rare occasions.

THE PROSTATE GLAND

INFLAMMATION

Inflammation of the prostate, or prostatitis, is most frequently secondary to posterior urethritis. Sometimes, however, it occurs in other ways, such as metastatic involvement in general pyemia or other forms of infection. Inflammations in the vicinity and direct injuries of the prostate may likewise cause acute inflammation.

Pathological Anatomy.—A simple and a suppurative form may be distinguished.

Simple Prostatitis.—In the ordinary prostatitis following urethritis the disease takes the simple form, the gland being congested and swollen and causing by its enlargement more or less obstruction of the urethra. Small suppurative foci may be formed in and about the glandular pouches and tubules. Catarrhal changes are seen in the tubular mucosa.

Suppurative or phlegmonous prostatitis, or abscess of the prostate, may be a terminal condition of the previous form, or it may be developed primarily. In cases of metastatic prostatitis a number of foci of supuration may occur and subsequently coalesce, or a diffuse suppurative infiltration may take place. The development of abscesses is usually acute, though in some cases it may occur insidiously. If the abscesses are small they may subsequently undergo encapsulation, inspissation, and even calcification. Larger abscesses are prone to rupture into the urethra, usually through a number of openings. Sometimes, however, the inflammation extends to the tissues around the gland, causing *peri-prostatitis*, and later rupture into the rectum may occur. Extensive phlegmonous inflammation of the pelvic tissues is an unusual result.

Chronic prostatitis is usually a companion of long-standing gonorrhea, and may assume a catarrhal or interstitial form. The catarrhal is more common, but there is always some indurative change. There is a thick, mucopurulent secretion in the tubules, which may dilate or coalesce by degenerative softening of the interstitial tissue.

ATROPHY AND DEGENERATION

Atrophy of the gland is occasionally met with in youthful individuals, and may be the result of disease or removal of the testis. It also occurs in the aged, and in this case atrophy of the tissues surrounding the prostatic ducts may be accompanied by dilatation of the ducts themselves, the gland then presenting a cavernous appearance. Atrophy of the gland sometimes leads to incontinence of urine.

Fatty degeneration of the epithelium of the gland and of the muscle-fibers is frequent in old age, and may occur as an independent condition or in association with hypertrophic enlargement of the gland. The gland becomes soft and diffusely yellow or mottled in color.

CONCRETIONS

Prostatic concretions are not unusual in persons of advanced age, and are frequently found in considerable numbers. They vary in size from almost microscopical granules to bodies the size of a millet-seed. They may be colorless at first, but usually become brownish. On section through the gland these brownish-colored bodies give the appearance of a surface sprinkled with snuff. The granules are usually round or oval, and are characterized by concentric lamellations. The term *amylaceous bodies* has been applied to them, and they have been supposed, though erroneously, to be composed of amyloid material, such as occurs in amyloid degeneration. Sometimes they reach considerable size, when calcareous salts deposit around them and give them an irregular form. Sometimes the concretions are discharged through the prostatic ducts into the urethra; in other cases the larger concretions project prominently into the urethra beneath its mucous membrane.

INFECTIOUS DISEASES

Tuberculosis of the prostate is usually found in association with tuberculosis of the other genital organs, especially the vas deferens and epididymis. It is also met with in association with tuberculosis of the bladder or kidney. The prostate is usually diffusely enlarged, and may be somewhat nodular upon the surface. On section caseous areas are found, or the entire gland has a caseous appearance. Recent tubercles are rarely visible, as caseation progresses with unusual rapidity in this organ. Primary tuberculosis of the prostate is rare.

HYPERTROPHY AND TUMORS

Hypertrophy of the prostate is a condition of clinical and pathological importance because of its common appearance after the age of fifty, the frequency of consequent cystitis and ascending infections, and the invalidism it occasions. Practically all hypertrophies of the prostate will fall into two divisions: first, those due to inflammatory disease, either primary or by obstruction and extension from the urethral outlets of the gland, and, second, those due to a more or less distinct tumor growth of some of the constituent tissues of the organ. In some cases chronic posterior urethritis seems to be the important factor; in other instances disturbances of the circulation, and especially varicose conditions of the veins, are active in the causation.

The organ may enlarge in a uniform manner, or there may be nodular or localized swelling. Of the localized form the most important, from a

clinical aspect, is that in which the middle lobe or the isthmus of the gland enlarges and projects under the posterior wall of the urethra as a small or large rounded elevation, or as a transverse bar or obstruction (Fig. 402). According to the investigations of some authorities, the enlargement in such instances is due to a hyperplasia of accessory prostatic tissue lying immediately under the mucous membrane of the bladder and of the prostatic portion of the urethra, with subsequent involvement of the isthmus of the gland itself.



Fig. 402.—Hypertrophy of the prostate. Seen from within bladder.

On section through the gland there may be a uniform induration, or in other cases, in consequence of associated changes in the epithelium or acini, there may be scattered through the gland areas of softening or of proliferation of the glandular elements, or cystic distentions of the gland tubules. In such instances the indurated gland presents more or less softened or cystic foci.

Microscopically, in the diffuse form, involving the stroma alone, the gland presents merely the features of uniform fibromyomatous proliferation, and corresponds in structure with fibromatous or myo-

fibromatous tumors of the uterus (Fig. 403). In other cases the glandular elements take an active part in the pathological process, and a distinctly adenomatous character is added. There is usually some interstitial round-cell increase, a condition suggesting that inflammatory lesions are associated, whether or not they are primary. The glandular elements may undergo fatty degeneration, and the lumina of the acini and tubules may be filled with milk-like, fatty material. In other cases pronounced cystic distention of the gland occurs.

Results of Hypertrophy of the Prostate.—Enlargements of the prostate usually interfere with the discharge of urine. This is particularly marked in cases in which the middle lobe projects into the urethra, though in some instances the opposite result may be produced, viz., incontinence of urine due to interference with the contractions of the

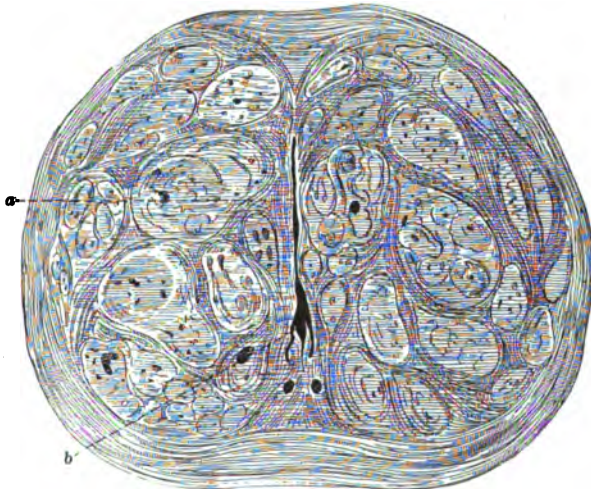


Fig. 403.—Section of hypertrophied prostate of a man aged seventy-four years; natural size: a, Urethra; b, colliculus seminalis (Socin).

sphincter of the neck of the bladder. In cases of enlargement of one of the lateral lobes obstruction to the flow of urine is caused by lateral deviation and compression of the urethra. Upward and forward projection of the middle lobe forms a reservoir in the postero-inferior part of the bladder, where fermentation and infective cystitis may begin.

The muscular walls of the bladder at first become hypertrophied, but dilatation of the bladder subsequently occurs. Cystitis, distention of the ureters and renal pelves, and ascending infection, causing ureteritis, pyelitis, and pyelonephritis, are among the late results.

Sarcoma is a rare tumor of the prostate. It generally has the characters of lymphosarcoma, and is a rapidly growing, destructive tumor. In some cases combination with adenoma has been observed. Sarcoma is, indeed, rarely pure in type, myomatous elements being commonly present. This tumor is commonest in childhood.

Carcinoma of the prostate is more frequent than sarcoma, though it is not a common tumor. The tumor arises from the epithelium of the tubules, and takes the form of nodular, grayish or white masses which cause irregular enlargements of the gland, and not rarely project into the urethra or the base of the bladder. The cells of prostate cancers are quite small and stain rather deeply, giving an impression of sarcoma cells. Superficial ulceration of the mucous membrane over these projections is not infrequent. The stroma of the gland usually proliferates actively. Metastasis to the inguinal glands, or to distant parts, especially the *bones*, is not infrequent; but direct extension to the bladder, seminal vesicles, or rectum is more common. There may be frank adenomata of the prostate; these are usually associated with or the cause of "*hypertrophy*."

Cysts of the prostate are usually the result of retention of exudates within the glands or their ducts. Occasionally, cystic formations seem to arise from remnants of Müller's ducts.

COWPER'S GLANDS

Inflammatory conditions are met with in these glands in association with similar affections of the prostate. Occasionally, independent inflammation of Cowper's glands results from posterior urethritis. The gland is enlarged and presents the usual appearances of inflammation. The termination may be abscess-formation. Obliteration of the mouths of the ducts may occasion cystic conditions in the glands, and carcinoma has been described.

THE SEMINAL VESICLES

Inflammation.—*Acute inflammation* of the seminal vesicles may occur in association with gonorrheal urethritis. The vesicles become distended with seminal secretion and mucopurulent exudate. Their walls are swollen, and the mucous membrane presents the appearance of catarrhal inflammation.

Chronic inflammation may result from the acute form; it causes contraction and thickening of the walls.

Tuberculosis of the seminal vesicles is common in cases of urogenital tuberculosis. The vesicles are rarely independently affected. The walls become thickened and may present nodular, cheesy masses, and there may be ulcerations of the mucous surface. The cavities of the vesicles contain caseous or puriform material.

Tumors.—*Primary carcinoma* has been described; but *secondary carcinoma*, resulting from extension of cancer of the adjacent structures, is more common.

Cystic distention and the formation of *diverticula* result from obstructions of the ejaculatory duct. The contents of the vesicles in such cases are seromucous in character.

Concretions frequently result from calcification of inflammatory exudates. They are especially frequent in association with tuberculosis.

THE MAMMARY GLANDS

CONGENITAL ABNORMALITIES

Absence of one or both breasts may occur in association with other defects of development of the thoracic walls. Incomplete development of the mammary glands, or hypoplasia, may be associated with hypoplasia of the genital organs.

Supernumerary mammary glands are frequently observed; the term *polymastia* is given this condition. The supernumerary gland or glands may be situated between the normal glands, below these, or in distant parts, such as the back, shoulders, and arms. They may occur in either sex, and may be structurally complete and functionally active; or may be merely rounded masses of mammary tissue without excretory ducts or nipples. In the latter instances the probable explanation of the condition is that in the process of development parts of the normal glands have been split off and have separately developed.

Early Development.—The mammary glands may be developed at an abnormally early period, in association with early development of the genital organs.

Abnormal functional activity (secretion) may be stimulated by various diseases of the genital organs; and in the newborn of either sex during the first week of life slight secretion of colostrum-like material is frequent.

Abnormal development of the male breast is occasionally observed, especially about the age of puberty, and sometimes copious secretion of milk takes place. Usually the organ subsequently atrophies, but exceptionally the enlargement and secretion persist.

CIRCULATORY DISTURBANCES

Hyperemia occurs during the menstrual period and at the beginning of lactation, as a physiological process, and causes slight swelling and redness. Pathological hyperemia plays a part in the process of inflammation.

Hemorrhages are usually the result of traumatism. They may occur into the gland itself, or into the connective tissue in front of or behind the gland. Occasionally, hemorrhages are due to intense inflammation or to tumor-formation. The blood may find its way into the lactiferous tubules, and may be in part discharged from the nipple. In case of large hemorrhages the blood may subsequently undergo absorption or inspissation, and hemorrhagic cysts may be formed. Occasionally, hemorrhage occurs in the mamma and from the nipple at the time of the menses, as a form of vicarious menstruation or in cases of dysmenorrhea.

INFLAMMATIONS

Acute inflammation of the mammae, or **acute mastitis**, is rarely met with, excepting during the puerperium. Exceptionally it may occur in cases of general pyemia, or in the newborn as a result

of active secretion and obstruction to the outlets. Sometimes inflammation of the glands results from direct extension of inflammatory processes of the skin, subcutaneous tissue, or thoracic walls. Puerperal mastitis is infective in character, and results from injury or disease of the nipple, through which the infective agents enter the glands. The actual portal of entrance may be the discharging tubules, or fissures and erosions of the nipple. Various micro-organisms have been discovered, including staphylococci and streptococci, of which the latter is the more common, especially in the puerperium.

Thelitis, inflammation of the nipple, is common in nursing women when they are at all uncleanly, since the act of sucking favors the production of small wounds. The inflammation of the mamma following thelitis is usually catarrhal, but may be interstitial.

Pathological Anatomy.—The gland is swollen and distends its capsule tensely, the skin is reddened, and a general hyperemia of the gland is noted. During the earlier stages the inflammation may be localized or may be diffuse. In the former case more or less circumscribed induration is discovered, while in the latter the organ is uniformly indurated. The tendency of mastitis is to terminate in suppuration. On section through the gland areas of light-yellowish color indicate the purulent infiltration, while in the later stages more or less extensive abscesses are formed. The latter may communicate with the lactiferous tubules, and pus and milk may be discharged from the nipple. The abscesses tend to extend in various directions, and may finally rupture upon the surface through fistulæ. After discharge of the pus granulation tissue is formed, and the cavities are obliterated by cicatricial tissue. When the larger discharging tubules are opened by the abscesses fistulæ may be formed, which continuously discharge milk. Small collections of pus may become encapsulated and inspissated, being converted into cheesy or partly calcified matter.

The connective tissues around the mammary gland are sometimes involved by extension, and suppurative or necrotizing *perimastitis*, or retromammary abscess, results. Extension to the thoracic walls and pleura is rare.

Chronic Mastitis.—Diffuse induration of the mammary gland, resembling in its histological features the indurative or chronic interstitial inflammations of other organs, is occasionally seen in middle-aged or old women. The causes are obscure, and it is difficult to distinguish some of the cases from certain forms of fibromatous tumors. The gland becomes hardened and sometimes slightly increased in size. In other cases retraction of the connective tissue causes a reduction in the size. On section firm bands of connective tissue are conspicuous, and the lactiferous tubules may be distended, forming small or large retention cysts. This form of disease will be further discussed under Fibroma.

ATROPHY AND HYPERTROPHY

Atrophy of the gland occurs as a physiological process after the menopause, or it may result from local causes, such as abscess or tumor-

formation. Artificial menopause, following oöphorectomy or diseases of the reproductive organs, may occasion atrophy similar to that normally present in old age. The gland may simply decrease in size, without notable change of any other kind. Sometimes, however, connective-tissue hyperplasia accompanies the atrophy of the glandular elements, and diffuse infiltration may occur.

Hypertrophy of the gland is sometimes met with in girls at the age of puberty, and leads to a uniform enlargement of the organ. In some cases there is a true hypertrophy of all the constituents of the gland; in other instances dilatation of the lymphatic channels, or degenerative changes, may cause a simulation of true hypertrophy. Both breasts, as a rule, are affected, and there may be increased functional activity (*galactorrhea*). Vicarious hypertrophy of one breast may occur after loss of the other.

DEGENERATIONS

Fatty infiltration, or **lipomatosis**, of the gland may accompany atrophy of the secreting tissue, or may occur as an independent condition. The gland may be greatly enlarged. Accompanying this infiltration there is usually diffuse hyperplasia of the connective tissue.

Myxomatous degeneration may be associated with fatty infiltration.

INFECTIOUS DISEASES

Tuberculosis of the mammary gland may be associated with tuberculosis of the axillary glands, or of other parts, or rarely may be primary. The tubercle bacilli reach the gland either through the lactiferous tubules or through the blood. The disease is characterized by the formation of distinct tubercles, which tend to unite and form caseous areas. There is rarely extensive disease.

Syphilis, in the form of gummata, is sometimes met with in acquired or congenital syphilis. Chancres or mucous patches may occur on the nipple.

TUMORS

Fibroma may be met with in the form of circumscribed nodular growths, or, according to the view of some pathologists, as a diffuse process. Circumscribed fibroma presents itself as a hard, nodular tumor, often having a distinct capsule, and on section presenting a lamellar arrangement. The glandular elements of the organ in the area of invasion may undergo secondary hyperplasia, and thus a form of **fibro-adenoma** may be developed. In the cases termed *diffuse fibroma* the entire organ may be indurated, or nodular areas of sclerosis may be found in various parts of the gland. The fibrous tissue may appear around and compress the glandular structures (*pericanalicular fibroma*), or the acini and ducts may at the same time undergo proliferation,

forming adenomatous structures; or compression of the ducts may lead to retention cysts (cystadenofibroma). It is difficult to determine in some cases whether the process is one of tumor-formation or one of inflammatory hyperplasia.

A form of particular interest is that known as **intracanalicular fibroma**. In this the proliferating fibrous tissue projects into the normal or dilated tubules in the form of papillary ingrowths. The mucosa lining the tubules is pushed forward by the ingrowths, and covers these in the same manner as epithelium covers superficial papillomata of the skin or mucous membranes. At times the epithelium proliferates extensively; this may be due to inflammation or to an adenomatous change in the mucosa. The gland may be greatly en-

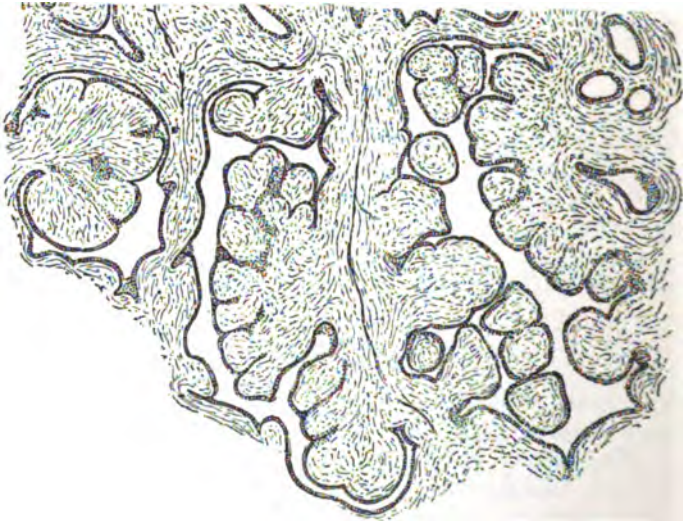


Fig. 404.—Intracanalicular fibroma of the mammary gland (Kaufmann).

larged, and on section presents an appearance resembling that of a cut through a cauliflower (Fig. 404).

Lipoma of the mammary glands occurs in the form of round, encapsulated tumors of the interstitial or periglandular connective tissues.

Myxoma may occur in a diffuse form, causing a transformation of the gland into myxomatous material, or as circumscribed tumors.

Myomata containing smooth muscle-fibers, and mixed tumors containing striated muscle-fibers, are rare.

Chondroma and **osteoma** have been observed.

Sarcoma is most frequently of the round-cell variety. It occurs in a diffuse form or as circumscribed nodules; association with fibroma and myxoma is not infrequent.

In *diffuse sarcoma* the gland undergoes a uniform enlargement, and the neoplasm extends rapidly, forming attachments to the skin

and sometimes causing superficial ulceration. In other cases extension toward the chest walls may occur, finally involving the pleura. On section through the gland a lobular character of the tumor may be recognized, and areas of fibrous or myxomatous character are visible here and there. Cystic conditions, sometimes met with, may be due to obstruction and consequent distention of the lactiferous tubules. The term *cystosarcoma* is appropriately applied to such cases. The sarcomatous tissue may project into the dilated tubules in a polypoid form (*intracanalicular sarcoma*). Section through the gland in such cases presents an appearance not unlike the surface of section of a head of cabbage. Cysts may also be formed in sarcomata by degenerative softening.

Localized sarcomata occur as nodular tumors arising from the connective tissue surrounding the acini. On section through the tumor the glandular acini may be seen within the nodules.

In any form of sarcoma the epithelium of the tubules and acini may undergo secondary proliferation, when the term *adenosarcoma* is applicable.

Adenoma.—Most of the tumors of the mammary gland are associated with some change in the secreting tissue, and it is often difficult to estimate how large a part this plays in the new growth. Degeneration or hyperplasia of the epithelium and obstruction of the lumen are the common alterations. Constriction of the ducts leads to cyst formation, and the process is little different when caused by chronic inflammation or neoplasms. In the tumors beginning as adenomata or with this type dominant, the acinous grouping is retained in those parts not becoming cystic, while in sarcoma or carcinoma any progressive change in the acini is atypical.

Adenoma of the mammary glands may be an independent growth, or may be associated with fibroma, sarcoma, or other tumors. The independent form presents itself as a circumscribed, encapsulated, nodular tumor, somewhat firmer than the substance of the normal gland. Microscopically, adenoma follows the tubular or acinus architecture, there being increase of the ducts or secreting areas respectively. These are usually somewhat dilated, and the epithelial cells are larger than those of the normal gland (see Fig. 81). Instead of a single layer of columnar cells, active hyperplasia may cause a complete filling of the acinus or duct with epithelium. Fatty degeneration of the cells is not infrequent, and sometimes there is a certain amount of milk-secretion, causing additional distention of the cavities. Great distention of tubules and acini produces *cystadenoma*. Papillary outgrowths of the mucosa taking place within dilated ducts or acini give rise to *papillary cystadenoma*.

Carcinoma may develop from the tubules or from the acini of the glands. It may begin as an adenomatous tumor, which subsequently undergoes carcinomatous transformation, or may be a typical glandular cancer from the beginning. In the cases primarily adenomatous the structure of the acini becomes atypical and the epithelial cells tend to

penetrate the *membrana propria* and form irregular collections or columns in the interstitial tissue. Degenerative changes are often observed, among which fatty degeneration is most frequent. Mucoid degeneration and a form of caseation are sometimes met with, and calcification may take place in the interstitial tissues. Occasionally an attempt at formation of milk occurs in the cancer-acini.

Varieties.—Among the varieties of carcinoma are the squamous, medullary, the simple, the scirrhus, the myxomatous, and the so-called adenocarcinoma.

The **squamous carcinoma** begins as an epithelioma of the nipple, or Paget's disease. The process proceeds by extension into the discharging tubules and penetrates the gland structure.

Medullary carcinoma, or **soft cancer**, is characterized by its softness and the abundance of liquid (cancer-juice). It grows rapidly and soon



Fig. 405.—Ulcerated carcinoma of the breast.

invades a large part of the gland, and attaches itself to the skin, which may finally be broken, exposing an ulcerated surface (Fig. 405). Actual inflammatory changes terminating in suppuration are not infrequent. The nipple is not retracted.

Scirrhus cancer is slower in growth, and is usually very hard; the skin is firmly attached to the tumor, and the nipple is usually retracted. On section the tumor is found to be of a firm, fibrous, and somewhat translucent character; extensions of the growth are seen radiating in various directions from the body of the tumor. Microscopically, the growth consists of fasciculated connective tissue, enclosing round or elongated collections of cancer-cells (see Fig. 89).

Simple carcinoma stands between the medullary and the scirrhous forms in point of hardness, as well as in point of malignancy. The three forms differ only in the relative amount of epithelial elements and fibrous tissue.

Myxomatous, colloid, or gelatinous cancer is a rare form in which the interstitial connective tissue suffers mucoid change, and the epithelial cells of the cancer-acini undergo more or less fatty or exceptionally mucoid degeneration (see Fig. 90).

Adenocarcinoma presents the general type of malignant adenoma. It may be solid or cystic or cystopapillomatous. It grows rapidly, and may go over into the soft or hard types.

Malignant papillomata of the ducts have been seen. These may become extensive and carcinomatous. Hemorrhage into the ducts or through the nipple is common from them.

Results.—Cancer of the breast may extend directly to the subcutaneous tissues and skin on the one hand, causing an indurated growth (cancer en cuirasse), or to the walls of the chest and pleura on the other hand. Metastasis frequently takes place through the lymphatics, the axillary glands, as a rule, presenting the first evidence of the extension of the growth. Secondary growths are often found in the pleura and bones. Malignancy varies directly with the softness of the tumors, the scirrhous form frequently having a comparatively benign character. Sometimes the increasing growth of connective tissue in this variety leads to practical cessation of the growth of the tumor.

Mammary cancers are much more frequent in the female than in the male sex. They are commonly met with after the age of forty, and traumatic influences seem to bear some relation to their occurrence.

Cysts.—Repeated reference has been made to the retention cysts of the lactiferous tubules caused by compression or other forms of obstruction. The gland may present a few or many cystic cavities about the size of a pea, containing whitish or milky liquid. Occasionally the contents of the cysts are cheesy (*atheromatous*). Distention of the acini of the glands in consequence of obstructions to the outflow of milk may lead to large cystic tumors containing milk (*galactocoele*). In the later stages the contents of such cysts may become thickened or caseous.

CHAPTER IX

DISEASES OF THE BONES

Anatomy and Development.—Bone is a dense form of connective tissue, the cement substance being impregnated with lime-salts. It may be spongy or compact in character. On transverse section one sees certain oval openings, surrounded by concentric lamellæ of a substance containing lime-salts. Each opening is the end of a so-called Haversian canal, which with the surrounding lamellæ forms an Haversian system. The areas between the Haversian systems are filled with osseous tissue not arranged concentrically. Between the lamellæ of bony tissue are seen irregularly oval spaces—lacunæ—from which run branching canaliculi. In preparations of fresh bone the lacunæ are found to be occupied by the bone-cells, which are irregular and have branching projections extending some distance into the canaliculi. In the center of the bones are found hollow spaces containing the bone-marrow. This is a vascular tissue, in the meshes of which are found large and small rounded cells resembling the lymphoid cells, red corpuscles, ordinary leukocytes, and some nucleated red corpuscles. A form of cell of particular interest is the large multinucleated giant cell, or myeloplaque. The marrow extends in the form of projections into the substance of the bone and communicates with the Haversian canals.

Surrounding the bone is the fibrous periosteum. This consists of a dense outer layer and a more cellular inner one, which is osteogenetic in function.

Development.—The beginning of the change of the original cartilage into bone consists in the multiplication of the cartilage cells and their arrangement in longitudinal rows. They grow into cartilage corpuscles of considerable size, calcification at the same time occurring in the matrix between these cells. Simultaneously, vascular projections extend inward from the perichondrium; the cartilage cells and preliminary calcareous deposit are subsequently removed, primary marrow-spaces being thus formed. Bone-cells are deposited in the spaces between the original cartilaginous trabeculæ, and at once begin to cover themselves with bony deposits, the cartilaginous trabeculæ gradually diminishing by absorption. By these processes a spongy form of bone is developed. Subsequently the concentric calcareous lamellæ of the Haversian systems are deposited within the spaces, and the spongy bone is thus converted into the dense form.

DISORDERS OF DEVELOPMENT

Many congenital defects of development are observed, such as the appearance of supernumerary bones, the absence of certain bones, the

failure of union between epiphyses and diaphyses, etc. These conditions are of little pathological interest. One condition of considerable interest (rachischisis) is considered on page 933.

The most important developmental disease is rickets.

Congenital rickets, or *chondrodystrophia fetalis*, or *achondroplasia*, differs in some respects from the disease met with after birth. The extremities are short and thick, the ends of the bones enlarged, and the shafts bent. The hand is curiously like a trident by reason of wide separation of the second and third fingers. There is increase of the original cartilage and of the periosteum, with an arrest of development of the bones. Subperiosteal bone formation is about normal, but epiphyseal growth is imperfect and the bones do not develop to their normal length. The cause is obscure, but the condition seems hereditary. The disease is essentially one of disproportionate or irregular ossification of already mapped out cartilaginous parts. It begins early in fetal life, probably in the second month. The thyroid shows overgrowth of alveolar epithelium and connective tissue, the former surrounding the latter, with the formation of separated islands of acini.

Closely related to the above is *osteogenesis imperfecta*, which, as its name implies, is an ossification short of completeness. The characteristic is to be found in the skull, where only small plates of bone are laid down, and these fail to unite to form the large flat bones. This may be a hereditary condition. It probably is due to delayed action of the periosteum, so that the shafts of long bones are imperfect and multiple fractures are common. *Fragillitas ossium*, or generalization of this, is discussed on page 848.

The effect of all these malformations is to render adjacent parts liable to damage and to favor fracture of the bones themselves.

RICKETS

Definition.—Rickets, or rachitis, is a constitutional disorder, attended with abnormal developmental processes in the bones, of which active proliferation of the cellular elements and lack of normal calcification are the most important.

Etiology.—The causes of rickets are still very obscure. The disease is in some way connected with improper nourishment, though there is probably also an inherited disposition, or a constitutional condition expressing itself chiefly in an inability of the primary cartilage to absorb calcium salts and ossify normally. It has been sought to establish a connection between rickets and syphilis, but any such relation is doubtful. Various chemical theories have been offered in explanation, a very ably defended one being that in some way calcium is eliminated in excess instead of being absorbed; the normal or very slightly reduced alkalinity of the blood in rickets speaks rather against this assumption. Formerly, it was supposed that the presence in the digestive tract of lactic acid in excess prevented the proper absorption of calcium; this theory, however, is generally abandoned. It does not

seem that reduced calcium intake causes the disease, because experiments with low calcium diet do not produce rickets in young animals. Ribbert now asserts that the cause is toxic, the poison producing degenerations in the cartilage-cells. The disease occurs in infants during the first year of life, and continues during the second and third years, after which the active manifestations subside.

Pathological Anatomy.—Rickets leads to various deformities, principally situated in the long bones and skull. The epiphyses, as those of the wrist, ankle, etc., are swollen, and in more advanced stages the shafts of the long bones may be variously distorted.

Sharp bends (*infractures*) may be observed in the long bones, and complete fractures may occur. The alteration of the skull is characteristic. The head is large and square in shape, the forehead prominent, and the fontanels remain open a long time. Osteophytes may form, and not rarely areas are found in the temporal or other bones in which the mineral substance is deficient or almost completely wanting (*cranio-tabes*), the spaces being filled by a parchment-like membrane. Deformities of the chest are frequent, the chicken-breasted condition being the most marked. In the beginning of the disease slight enlargement of the



Fig. 406.—Rachitic enlargement of the end of a rib (modified from Bollinger).

ends of the ribs at the junction with the costal cartilages, causing the beaded appearance called the "rachitic rosary," is observed (Fig. 406). Various distortions of the spinal column, flattening of the pelvis, and other deformities may be met with in marked cases.

The *minute changes* of rickets consist in a form of abnormal development, in which calcareous deposition does not progress in the normal manner, but is replaced by proliferation of the cellular elements. In consequence of this the bone presents irregular areas of partial calcification lying between portions made up of greatly proliferated and enlarged cartilage cells. Between the epiphysis and diaphysis of long bones there is a wide irregular bluish zone of imperfectly ossifying cartilage richly supplied with blood-vessels. Projections from the marrow and periosteum extend deeply and visibly into the body of the bone, which is thus composed for the most part of osteoid instead of osseous tissue. The marrow-spaces are irregular and excessive in size. These changes in the bone are marked at the epiphyseal extremities, and thus lead to the visible enlargements. It is thus seen that the process in rickets is failure of development of the normal structure, rather than absorption of existing bone. The original calcareous deposit around the cartilage cells is largely or completely absorbed, as in normal bone-

formation, and often even more rapidly. The subsequent deposit of calcareous bone does not form, but in place of it there occurs a rapid proliferation of cartilaginous and other cells.

When, however, the progression of the disease is stopped, calcification occurs as usual, although there is a tendency to extreme hardness of the bone, small Haversian systems, and excessive periosteal bone.

Associated Conditions.—The changes in the bones do not constitute the entire pathology of rickets. There are frequently gastrointestinal disorders, such as catarrhal inflammations of the mucous membrane. Proliferative changes are met with in the spleen and liver, leading to fibrous overgrowth and enlargement, and the blood is more or less profoundly altered. Decrease in the number of red corpuscles and leukocytosis are the conspicuous features. Nucleated red corpuscles may be found in more or less abundance, according to the grade of anemia, and the leukocytosis involves a special increase of mononuclear elements; a myelocytes may be present.

REGENERATION OF BONE

Regeneration of bone occurs most typically in the healing of fractures, and also as a part of various pathological processes in which a certain amount of destruction of bony tissue has taken place. Hypertrophy may be included in the same group of affections.

Fractures.—Definition.—Fractures are breaches in the continuity of bone which occur in consequence of direct force or of muscular contractions. The bone may be broken in various directions, the line of fracture being straight or irregular, directly transverse to the long axis of the bone, or oblique. The bone may be broken into a number of splinters (*comminuted fracture*), or the fracture may be a single one. There is always more or less injury to the soft parts immediately surrounding the bone, and sometimes extensive injury causes communication between the outer surface and the seat of fracture through flesh wounds (*compound fracture*).

Repair of Fractures.—The process of repair is much the same as the process in the original formation of bone. Immediately after the fracture there is more or less hemorrhagic extravasation within the marrow and around the broken ends of the bone. Within a few days cellular infiltration, with congestion and edematous swelling of the periosteum and marrow, as well as of the bones, may be noted. Proliferative changes then take place in the same situations and new blood-vessels are formed. The adult bone-cells do not regenerate bone, this process devolving upon the osteoblasts of the periosteum and marrow. They multiply and arrange themselves and their intercellular substance in a form similar to that of bone into which first cartilaginous, then osseous, matter is deposited. The condition of this tissue varies greatly in different cases; sometimes it is quite fibrous, in other cases almost purely cartilaginous. Gradually it is converted into bone by the regular processes of bone-formation. At this stage the seat of fracture is

occupied by a deposit of soft, bony material of considerable bulk, which causes a local thickening of the bone. Finally the excess (temporary callus) is removed by absorption, the parts in the direct line of the bone upon which the strain naturally falls become thickened (definitive or permanent callus), and other parts are absorbed.

The original deposit of osteoid or chondroid material at the seat of fracture is termed *callus* (Fig. 407). Part of this is deposited on the exterior (*periosteal callus*), and is derived from the periosteum; part is within the marrow cavity (*myelogenous callus*); and a third part is



Fig. 407.—Fracture of the femur, showing malposition of the ends of the bone and abundant callus (modified from Bollinger).



Fig. 408.—Fracture of humerus; section through the bone, showing the repair of the fracture (modified from Bollinger).

sometimes seen between the ends of the bone (*intermediary callus*). The last is produced by the periosteum.

The healing of fractures under the most favorable circumstances—that is, in cases in which the fragments of bone are restored to their proper position—is accomplished with but little disturbance of the normal relations. The seat of fracture may be permanently thickened, and there is always some shortening of the affected bone, when the fragments are not placed in proper position, or angular deformities may result with considerable thickening from deposit of bony material between the fragments (Fig. 408).

When the fragments are not kept in apposition, or when the general condition of the patient is unsatisfactory, the union of the fragments

may be prevented and "ununited fractures" result. The ends of the fragments in these cases become rounded by absorption of the sharp edges, forming false joints (*pseudarthroses*).

When ossification is imperfect fibrous union takes place.

Hypertrophy

Local or general hypertrophy of bone may be found. *Local hypertrophies* may occur in consequence of increased strain upon certain parts of a bone, either directly or through the muscles. In muscular individuals hypertrophy of this kind is frequently seen at points of attachment of the muscles. In cases of injury or incapacity of one of the limbs the other may show hypertrophy.

Giant growth of certain bones, or of the entire skeleton, may be observed. Local hypertrophy of this kind, dating from childhood, is especially common in the upper extremities, and is frequently unilateral. It may be observed as a bilateral condition in the fingers. Complete giant growth usually begins about the age of puberty. The individual, previously developed as others, begins to grow abnormally until an excessive size is reached. The bones are not only very large, but often markedly thickened and irregular.

Acromegaly is an allied condition in which giant growth of the hands and feet, forearms and legs, and parts of the face, notably the lower jaw and parts of the cranium, is observed. A certain amount of hyperplasia of the soft tissues in the affected region accompanies this change. Hyperplastic conditions, tumors, and other diseases of the hypophysis cerebri, especially of the anterior lobe, have been met with in a considerable proportion of the cases. In some of the skeletons of giants investigated with regard to this point enlargement of the sella turcica has been found, and this evidences the occurrence of enlargement of the pituitary body in some, at least, of such persons. The exact relation between pituitary disease and bony hypertrophies remains obscure. (See Hypophysis.)

CIRCULATORY DISTURBANCES

Hyperemia is normal during the development of bone, or may accompany inflammatory disturbances of the neighboring parts. The marrow becomes more or less light- or dark-red in color, and the periosteal vessels may be injected. The entire bone may have a pink or reddish color.

Thrombosis may occur in the blood-vessels of the marrow, giving rise to areas of degeneration or myelitis, or in the cancellated tissue at the ends of long bones, in which case it may be of importance in the production of osteomyelitis or arthritis if the thrombus be infective.

Hemorrhage beneath the periosteum and in the marrow is comparatively common. It may result from traumatic causes or from scorbutic or purpuric conditions, as well as from inflammatory affections

of the parts involved. Considerable subperiosteal hemorrhages are found in cases of infantile scurvy. The separation of the periosteum from the bone may lead to necrosis of the superficial layers of the bone. A similar accumulation of blood beneath the periosteum is that found over the bones of the skull in the newborn—the *cephalohematoma*. This results from the traumatism of labor. Large accumulations of blood of this nature may be absorbed or may undergo suppuration.

Hemorrhage into the substance of bone may accompany other diseases affecting it, such as caries, tumors, and the like.

INFLAMMATIONS

Periostitis

Definition.—Periostitis, or inflammation of the periosteum, may be of various forms, and may lead to different results. Sometimes the evidences of inflammation are very apparent; in other cases the disease appears in the form of a chronic productive process, leading to overgrowth.

Etiology.—Periostitis may be the result of traumatism, with or without the establishment of a communicating wound. In the latter case the injury provides an area of lessened resistance, which may subsequently become infected. In the former case the infection is direct, coming from the outside. Hematogenous infection without local injury is frequently observed. Infective periostitis may result from extension of an inflammation situated near the bones or from osteomyelitis. In all forms of bone disease more or less local periostitis occurs as a complication. In some cases the etiology is obscure, as in the periostitis which occurs during pregnancy and leads to the formation of osteophytes.

Pathological Anatomy.—We may distinguish simple, suppurative, and ossifying periostitis; the simple may pass into the severer grades.

Simple Periostitis.—The membrane becomes swollen, red, and sometimes infiltrated with blood. Microscopically, there are round-cell infiltration and proliferation of the periosteal tissue. If the process has been extensive and the irritation long continued, a termination in fibroid thickening may be observed. This is not unusual in cases of fractures.

Purulent Periostitis.—The disease may be circumscribed or diffuse. There are marked swelling and cellular infiltration, particularly in the deeper layers, and abscess-formation results. Separation of the periosteum from the bone ensues, because of the tendency of the pus to dissect between the bone and its covering; this may lead to local interruption of the circulation between the periosteum and the bone, and consequent superficial necrosis of the bone with exfoliation results. In the diffuse form of periostitis widespread areas of the periosteum may be quickly involved and rapid destruction takes place. In these cases a considerable inflammation of the surrounding tissues is customary. In all in-

stances there is a tendency to burrowing of pus toward the surface, and its eventual discharge. The retention of necrotic portions of the bone may lead to continued suppuration, but with removal of the dead portions healing usually occurs. Ostitis and osteomyelitis are very frequent results of periostitis; on the other hand, they may be in certain cases the original cause.

Ossifying periostitis leads to the formation of bony excrescences, exostoses, or osteophytes. There is first a proliferation of the osteogenic layer of the periosteum, then partial ossification, and finally complete bone-formation with firm attachment to the underlying bone. The osteogenesis is essentially the same, but the periosteal bone-depositing cells are working in a tissue the seat of productive fibrosis, so that the calcium salts are not laid down in an orderly manner along the surface of the bone. These changes may be circumscribed or diffuse, and cause irregular elevations or general thickening of the bone. The exudate may be merely fibrous tissue or a soft albuminoid material, usually leading to periosteal thickening, but occasionally involving the bone or the marrow. Occasionally the surrounding connective tissues are implicated (*parostitis*). Ossifying periostitis may occur in the vicinity of joints affected with chronic arthritis. It may occur as a result of diseases of bones attended with considerable destruction, such as tumors, tuberculosis, etc. Occasionally the causes are entirely obscure. An interesting form is that which occurs in the bones of the hands and feet, forearms, and legs in tuberculosis of the lungs and empyema, or more rarely in other diseases; to this the term *hypertrophic osteo-arthritis* has been applied. This is a form of osteoperiostitis of ossifying type, and it seems to be due to the action of circulating toxins developed in the diseases with which it is associated, or to chronic passive congestion. Perhaps both factors are important.

Associated Conditions and Results.—The conditions met with in the adjacent bones and other parts have been referred to. General infection and intoxication may follow upon the suppurative cases, and death may then occur from septicopyemia. Permanent thickening of the bone may result in any case, or resolution may be practically complete.

Osteomyelitis and Ostitis

Definition.—Acute osteomyelitis and ostitis are usually combined, and occur as an inflammatory condition affecting the marrow and its extensions into the communicating canals of the bone. The lamellar substance of the bone is only secondarily involved.

Etiology.—Osteomyelitis is an infective disease resulting from hematogenous infection in the course of various diseases, from local infections in cases of traumatism (fracture, amputation), or from periostitis. Various micro-organisms, including staphylococci, streptococci, typhoid bacilli, and the *Bacillus coli communis*, have been discovered. The so-called primary or idiopathic cases are frequently secondary to a boil or an angina, and occur commonly in adolescents.

Pathological Anatomy.—The marrow first becomes red and edematous, then cellular infiltration and proliferation are superadded, and finally collections of pus or diffuse purulent transformation follow. Large areas of necrosis appear in the marrow and in spongy bone because of the cellular infiltration and vascular thrombosis. The surrounding bone is involved,



Fig. 409.—Necrosis of femur, the result of acute osteomyelitis (Warren).

becoming more or less infiltrated, softening, and not rarely undergoing necrosis (Fig. 409). Small or large sequestra may be formed, or the bone may necrose completely. Periostitis is generally associated by extension through the Haversian system, and this layer is lifted from the bone, which thus deprived of nourishment from without undergoes rapid necrosis. The tissues around the bone are usually infiltrated and suffer suppurative or necrotic changes. The process extends to the spongy ends, and to the joint surfaces in severe cases, and the supuration cuts off the circulation. From here metastatic processes can arise from infected thrombi. Hypertrophic changes may occur in the periosteum and superficial layers of bone, causing a bony encasement (involucrum) of central sequestra. In such instances a suppurating sinus, extending from the bone to the surface, usually remains.

The rapidly developing cases of youth commonly begin as an epiphysitis, probably the result of infective embolic thrombosis; in fulminating cases there may be a general gangrenous myelitis.

Associated Conditions.—Implication of the neighboring parts is habitual—deep-seated abscesses, arthritis, etc. General infection is usually the final result, and commonly leads to a fatal end. Marked changes in the blood

have been observed—leukocytosis, with large proportions of large mononuclear cells, myelocytes.

Chronic Ostitis

Chronic inflammatory processes are more apt to involve the bone than the marrow, though the beginning of the disease may be frequently in the latter situation. It may be suppurative, degenerative, or hypertrophic in character.

Etiology.—Chronic ostitis may follow osteomyelitis and necrosis, necrotic sequestra keeping up a constant irritation. In these cases the disease is primarily infective. The chronic inflammations of bone due to tuberculosis and syphilis have special characters, which will be described below. In many cases the cause of chronic ostitis is obscure,

though probably circulating toxic substances are the specific factors. Direct traumatism, periostitis, or other inflammatory diseases surrounding the bone may be the immediate causes.

Pathological Anatomy.—In the necrotic and suppurative form, following osteomyelitis, there is more or less softening of the bony substance by absorption of the calcareous matter, and at the same time proliferation, in the form of granulation tissue, of the cellular elements of the marrow and its prolongations within the Haversian channels. Localized abscesses may be formed, or infiltration of pus in various directions with increasing necrosis of the intervening bone may occur.

The degenerative form of osteitis is a variety in which the calcareous matter is absorbed, and the bone thus rendered more soft and porous. The term *inflammatory osteoporosis* is applied to this. In the process of absorption there are formed upon the outer and inner surfaces of the bone, or within its substance, areas of erosion, hollow spaces or indentations, showing bone-corpuscles and giant cells lying upon the eroded bony tissue. These depressions are the so-called Howship's lacunæ. The giant cells, which are active in the absorptive process, are termed *osteoclasts*, and are anatomically identical with the osteoblasts or osteoplaxes of developing bone. It may be that the leukocytes of the burrowing pus are also able to produce absorption of bone structures. Simultaneously with this absorption of the lamellæ of bone there is proliferation of the marrow substance in the eroded areas, and at the same time there may be increased vascularization of this intervening tissue. Perforations are frequently established through the lamellæ by the penetration of new-formed blood-vessels, so that neighboring excavated areas communicate. This form of inflammation of the bone is frequent in the neighborhood of necrotic areas or osteomyelitic collections of pus, and plays a part in the pathological processes of osteomalacia and other bone diseases. It is rarely an independent condition.

The hypertrophic form of chronic inflammation leads to increased density of the bone, to which the term *condensing osteitis*, or *osteosclerosis*, is applicable. It may occur as a reactive process surrounding areas of osteoporosis or other local diseases of the bone, or in association with ossifying periostitis. Occasionally, it occurs in certain bones or parts of bones without local or well-ascertained general causes. Such cases are met with in syphilitic persons. The anatomical changes consist in the deposition of increased quantities of bony tissue by the same processes as are operative in normal bone-formation. It is, therefore, a process in which the reparative forces have gained the field, a reverse of rarefying osteitis. The lamellæ become wide, and the vascular spaces are encroached upon and sometimes wholly replaced by bony tissue; the osseous tissue which is laid down is very compact and the bone channels are narrow.

The disease designated as *leontiasis ossium* is a form of osteosclerosis affecting the bones of the head and face, and causing irregular thickening and enlargement of these bones. The cause of this condition is obscure.

Ostitis Deformans

Ostitis deformans is a condition which affects the skull, vertebræ, and certain long bones, causing enlargement of the affected parts and, on account of the elasticity of the diseased bony parts, great deformity. Fractures do not occur. Pathologically there is absorption of the compact bone, with confluence of the Haversian canals and new formation of osteoid tissue and fibrous tissue throughout the diseased structures. There is a deforming ossifying periostitis accompanying the internal absorption. The medullary cavities of the long bones are filled with vascular connective tissue and abundant fat-cells, and sometimes cysts containing gelatinous material are observed. Giant-celled sarcoma may occupy the medulla. The etiology of the disease is obscure, but some form of trophic disturbance undoubtedly plays a part in the causation.

DEGENERATIVE CONDITIONS

Caries

Caries is a term applied to the molecular destruction of bone, corresponding to ulceration of the soft parts. It may be associated with osteomyelitis, or with necrosis due to traumatism or various infective conditions. The changes consist in progressive softening and crumbling of the bone, with eventual destruction of more or less considerable areas. Caries is especially frequent as a part of tuberculosis of the bones, and will be described in connection with that disease.

Necrosis

Definition.—Necrosis is term applied to the death of a small or large portion of bone in mass.

Etiology.—Among the causes are the various acute or chronic diseases of the periosteum, bone-marrow, and adjacent bone. In cases of purulent periostitis the separation of the periosteum from the underlying bone leads to interruption of blood-supply and superficial necrosis. Similar results occur in cases of osteomyelitis. Necrosis of the bone may also occur in consequence of embolic obstruction of the blood-vessels.

Pathological Anatomy.—Necrosis may be *partial* or *total*, and may occur in the center of the bone or at the periphery. The dead portion of the bone, termed *sequestrum*, presents itself as an irregular, more or less eroded fragment, almost completely or completely separated from the remaining structure. The separation occurs by the process of demarcation, as in necrosis of the soft parts. This line consists of an area of absorption of the calcareous matter and proliferation of the cellular elements. The necrotic portion, or sequestrum, acts as a foreign body, and by its continued irritation keeps up a suppurative inflammation of the surrounding tissues. Fistulous communication

with the exterior is usually observed. If the sequestrum is peripheral and has been discharged, the periosteum or the bone may replace the lost tissue by regeneration. If the fragment is large or centrally placed, discharge is impossible and suppurative inflammation continues, sometimes for years. Bony tissue usually responds to the presence of a sequestrum by the formation of sclerosing osteitis and periostitis, and considerable hyperplastic material may be deposited over and around the sequestrum, and thus irregular thickening of the bone may be produced. At times, however, the continued irritation and suppuration may lead to complete destruction of all the bony tissue in the neighborhood.

A peculiar form of necrosis is that occurring in consequence of chronic phosphorus-poisoning. It is met with in persons engaged in the manufacture of phosphorus matches, and affects the maxillary bone. The existence of carious teeth aids in the development of this form of necrosis, probably by admitting micro-organisms which infect the bone already altered by the poison. The process begins in the periosteal and subperiosteal portions of the bone, and ends in more or less complete necrosis.

Associated Conditions.—Long-standing necrosis causes great deterioration of the general health, particularly in cases in which suppurating sinuses are formed. Systemic infections may follow and amyloid degeneration of various organs may occur.

HYPOPLASIA AND ATROPHY

Hypoplasia, or the lack of development of bones, may occur as a local or general condition. Local hypoplasia may be due to injuries or diseases which render a part of the body useless. General hypoplasia is found in cretins and dwarfs.

True atrophy of the bones may involve an entire bone or only portions of it. General atrophy of the whole or of parts of a bone occurs as a result of inactivity or want of use, as in cases of palsy, chronic rheumatism, and the like. The process is one of greater activity of the osteoclasts than of the osteoblasts. It may begin in the marrow canal and proceed outward, eccentric atrophy, or beneath the periosteum, concentric atrophy. The Haversian canals are widened and a condition of *osteoporosis* arises. The implication of certain parts of the nervous system (trophic centers) is particularly important, as the atrophy resulting in such cases is much more extensive than that occurring in cases of similar inactivity from other causes.

Partial or local atrophy of the bone may be due to pressure by aneurysms, tumors, and the like. In these cases there is gradual absorption of bony substance, and the process is really one of inflammatory osteoporosis.

General Atrophy.—Absorption of the bony substance, with resulting osteoporosis, may occur in marasmic individuals, particularly in seniles. In these cases it is held by most authorities that the pathological condition is dependent upon the failure of replacement of bone

to make up for the normal absorption constantly taking place. In these cases the bone becomes extremely fragile from the increase of its marrow-spaces and its general porosity. A condition of excessive fragility is termed *fragilitas ossium*, or *osteopsathyrosis*. Occasionally this condition of fragility is met with as an idiopathic disease, without definitely discoverable causation and without evident disease of the bones. Such cases have been found to occur in certain families through several generations.

Osteomalacia

Definition.—This disease is probably a constitutional condition leading to absorption of the bone-salts and to other changes in the bone, which cause extreme flexibility.

Etiology.—The causes of osteomalacia are still obscure. It is a disease occurring with especial frequency in puerperal women, but it may occur in men and in non-puerperal women. A number of theories have been offered to explain the disease, but none of them has been established. In some respects it seems not unlikely that it is a tropho-neurosis, based upon the fact that the removal of the ovary brings benefit in some cases. It is also thought that adrenal insufficiency plays a part, and treatment with adrenal extract has a good effect in some cases. Most authorities look upon it in pregnancy as an exaggerated natural process of giving up inorganic salts to the fetus. An excess of earthy material is excreted in osteomalacia. There is loss of calcium and increase of sulphur and magnesium in the bones during active osteomalacia. It is particularly frequent in certain regions (endemic), while in others it occurs very rarely (sporadic).

Pathological Anatomy.—The changes in the bone lead to various deformities and changes of appearance. Distortions, bends, and even fractures are observed in the long bones, and deformities due to abnormal curvatures of the spine are not infrequent. The shaft of the long bones may become of paper thickness. The pelvis shows peculiar changes which may prove very troublesome during labor. The characteristic change is a beaked condition, due to displacement forward of the pubes and a lateral indentation. This gives a triangular form to the outlet of the pelvis or superior strait. The bone-marrow is often quite red, and the periosteum in the neighborhood of bends or fractures may be thickened by cellular proliferation. The minute structure of the bone in osteomalacia shows a more or less pronounced absorption of calcareous matter, but the normal lamellar arrangement of the bone may be preserved. With the abnormal bone absorption there is a tendency to considerable deposit of osteoid material, but calcification of this substance is never completed. In the region of bends and fractures osteoid tissue of irregular structure, with bony corpuscles of considerable size, may be observed; while in other situations the regular lamellar arrangement and the ordinary small-sized bone-corpuscles are seen. Irregular areas of homogeneous or granular appearance may be interspersed within the normal osseous tissues. The line of demarcation between such

abnormal non-calcareous portions and the unaltered bone may be either sharply drawn or diffuse.

Associated Conditions.—Patients suffering from osteomalacia are usually reduced or cachectic, and frequently perish with terminal pneumonia. Some cases end in recovery by restitution of the bone. It has been claimed that there is evidence in all cases of puerperal women of some bony absorption, and osteomalacia, therefore, would seem to be but an exaggeration of normal conditions. Normally, the slight bony changes are corrected after the puerperal period is passed.

INFECTIOUS DISEASES

Tuberculosis

Tuberculosis may occur in bones in several forms. Miliary tubercles may be found in the bone-marrow in the course of general miliary tuberculosis, and local tuberculous disease of the periosteum may be met with. The most frequent and most important form of tuberculosis is tuberculous osteitis with caries.

Etiology.—The involvement of the bones is nearly always secondary, the first manifestations of tuberculosis occurring in other structures, notably the lymphatic glands and the lungs. The original focus of disease is, however, frequently small, and may remain quiescent while the lesion in the bones advances. The disease of the bones may be due to direct extension or to hematogenous infection. Not rarely the joints are first involved and the neighboring bones only secondarily; indeed, it has been said that tuberculosis first noticeably affecting the epiphyses spreads from lesions in the synovia of adjacent joints. The epiphysis of a long bone and the cancellated tissue of flat and irregular bones are much more easily affected with tuberculosis than the marrow of long bones. Doubtless, both the epiphysis and metaphysis may be infected from joint cartilages. Fraser suggests that the settling point of the tubercle bacillus may be an endarteritis due to tuberculous toxemia.

Traumatic influences are of importance in determining the situation of hematogenous tuberculosis. The traumatism causes circulatory disturbances in the bone, and thus produces a suitable soil for the bacilli to find lodgement. Bone tuberculosis is most frequent in early life; it may actually begin *in utero*.

Pathological Anatomy.—Tuberculosis attacks by preference the outer layers of the marrow, the spongy bony tissue, and the periosteum. In the last there is usually proliferative change with caseation, caries of the underlying bony layers, and fibrosis. The tuberculous lesion of bone first presents itself as an area of grayish color, with congestive reddening of the parts around and intense injection of the bone-marrow in its vicinity. Subsequently there are rapid cheesy change and more or less softening of the area of inflammation. Microscopically, tubercles in various stages of degeneration are discovered, and in addition areas of diffuse tuberculous granulation tissue and caseous degeneration

(Fig. 410). The marrow about the tubercle is at first the seat of diffuse hyperplasia which gives away to lymph-cell infiltration, and this is in turn followed by fatty and fibrous tissue overgrowth. Lamellar changes are at first in the form of rarefying osteitis with caseous infiltration, about which extension occurs and new foci are established. The entire diseased area may be separated from the uninvolved bone as a sequestrum, but more frequently there is gradual carious softening, with formation of semifluid, cheesy material containing gritty particles of bone or calcareous matter ("bone sand"). Complete softening leads to the formation of a "tuberculous abscess" (Fig. 411). In these cases a more or less irregular cavity is formed within the bone, the wall of the cavity being covered with a pyogenic membrane developed from the marrow and its extensions into the Haversian canals. The contents of

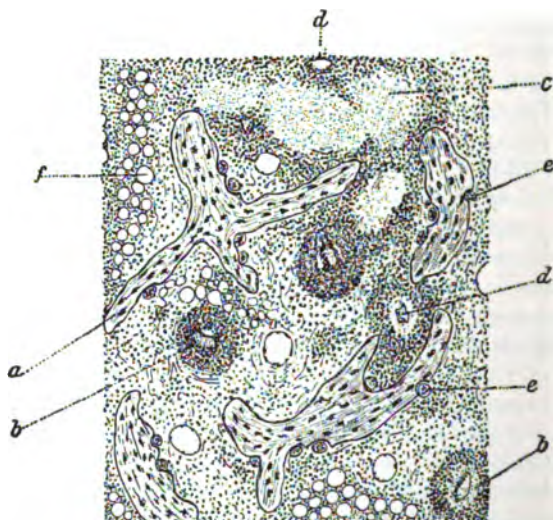


Fig. 410.—Tuberculous caries of one of the bones of the foot: *a*, Bony trabecula; *b*, tubercle with caseous center; *c*, caseation in a focus of tuberculous tissue; *d*, giant cells in tubercles; *e*, osteoclasts; *f*, fatty marrow (Kaufmann).

the abscess are puriform or cheesy. The process tends to extend to neighboring parts, particularly to the joints. When the abscess has penetrated the encasing bone it may spread within the soft parts, thus forming large tuberculous abscesses (so-called *cold abscesses*).

The periosteum reacts to the lesions within the bone by the formation of a productive periostitis, the new formation being either densely packed lamellæ or similar to spongy bone. An osteoporosis may appear beneath the periosteum when tubercles form on the under surface of that tissue.

Reactive changes may occur locally, and more or less restitution may take place. Complete encapsulation of a small focus may occur by the formation of a surrounding zone of granulation tissue and cicatrization, or by new formation of bone occurring after the activity of the tuber-

culous process has been arrested. When adjacent portions of articulating bones are involved the integrity of the articulation is disturbed, and subsequently ankylosis may be established by the formation of exostoses and their union. The spread of the lesions toward joint surface is favored by the predilection of the tuberculous process for the spongy bone at the epiphysis, where it is apt to cause infarct-like anemic areas by arteritis or phlebitis. Obliterating endarteritis is commonly seen near the lesions.

Some fairly distinct forms of bone-tuberculosis may be recognized pathologically, depending upon different combinations of the histological features above outlined. A large caseous tubercle may become encysted by fibrous tissue, but retain a sequestrum. There may be at times a diffuse puriform exudate without definite tubercles, but with rapidly advancing osteoporosis; this may possibly be due to mixed infection. There are also forms rather slow in their progress, the atrophic and hypertrophy, in which osteoporosis and osteosclerosis are respectively the predominating features.

Seats and Associated Conditions.—Among the bones more frequently affected are the vertebræ, the long bones, particularly the femur, and parts of the skull. In the vertebræ the bodies are generally affected, and angulation or distortion of the spine results (Pott's disease). The cold abscesses formed in these cases may burrow considerable distances, pointing far below the place of origin. Those springing from the cervical vertebræ may point beneath the mucous membrane of the pharynx or esophagus, or anteriorly in the neck above the clavicle or shoulder. The abscesses formed in tuberculous caries of the dorsal vertebræ may point under Poupert's ligament. Tuberculous disease of the petrous portion of the temporal bone is not infrequent following tuberculous disease of the ear; it is important as a possible cause of tuberculous meningitis. Tuberculosis of the head of the femur and of the hip-joint is one of the most frequent forms of surgical disease in children. The phalanges are sometimes involved in early childhood by a curious form of tuberculosis, in which the shaft of the bone increases in size by gradual absorption and tuberculous softening within and deposition of new bone from the periosteum without.



Fig. 411.—Tuberculous "abscess" in the lower end of the humerus (modified from Bollinger).

Syphilis

Syphilitic disease of bones may appear in various forms. Allusion has already been made to the condensation of the bones, or osteosclerosis,

in this disease. Syphilis may also occur in the periosteum as a nodular periostitis, or in the substance of the bone in the form of degenerating gummata. Congenital syphilis gives rise to certain peculiar alterations.

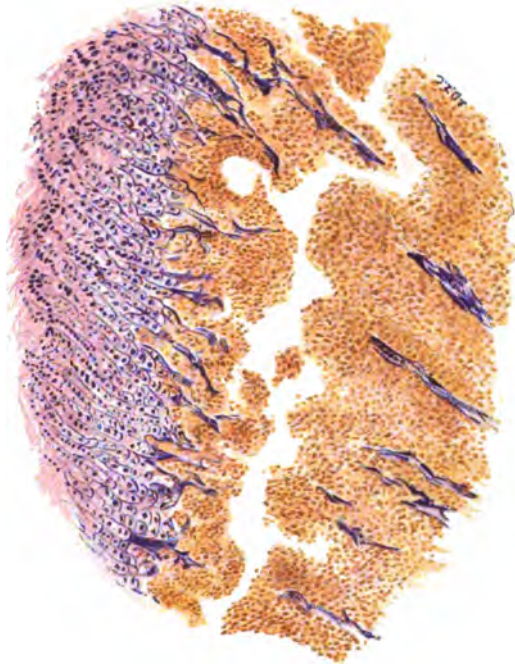
Etiology.—Syphilitic changes in bone are confined almost exclusively to the tertiary period. They may occur without other luetic disease, or as concomitants of hepatic, splenic, or other visceral disorders. The disease of the bones is frequently determined by local injuries; especially is this true of the periosteal forms.

Pathological Anatomy.—*Syphilitic periostitis* is very common upon the shin-bone, less frequent in the periosteum of other long bones. There is, first, slight swelling of the periosteum, due to multiplication of the cells. Subsequently, this cellular mass undergoes cheesy or mucous degeneration, and the mass presents the appearance of a small gumma. Superficial erosion, or even necrosis, of the bone may take place, and discharge of the contents may occur. Following this, hypertrophic processes in the bone and adjacent periosteum lead to the formation of bony nodes. These nodes may, however, be formed without the occurrence of softening and discharge from the periosteal lesion, the process in this case being one of simple ossifying periostitis. *Gummata* of the bones generally begin in the deeper layers of the periosteum, but tend to involve the bone more extensively than the form just described. The gummatus infiltration and proliferation occur along the blood-vessels of the periosteum and extend into the substance of the bone. Considerable areas may thus be implicated. The bone itself is absorbed, or may undergo rapid caries or necrosis, with weakening of the bone, but with little tendency to sequester formation. Around the area of syphilitic change may occur a zone of reactive hyperplasia of the bone and periosteum. This may take the form of ossifying inflammation, giving rise to diffuse hardening of the shaft or of the layers directly under the periosteum, or hyperostoses may develop. The gummata themselves become cheesy or undergo mucoid degeneration, and eventually may discharge upon the surface. Syphilitic gummata are most frequent in the bones of the head, tibia, and sternum.

Occasionally, gummata arise in the marrow of the bones instead of in the periosteum.

Congenital Syphilis.—The bony changes of congenital syphilis are quite characteristic. The virus attacks the fetal cartilage, causing an irregular proliferation as a sort of granulation tissue and the deposit of bone salts without proper arrangement. The alterations occur at the junction of the epiphyses with the diaphyses of the long bones. Longitudinal section through these parts shows the line of junction as a bluish-white or yellowish-white irregular zone about 2 or 3 mm. in thickness (Plate 14). In more advanced stages this line becomes thicker and more yellow. The epiphyses may be completely separated from the shaft. The minute changes consist in proliferation of the cartilage-cells and fatty degeneration, about which bone is laid out irregularly the spaces between the lamellæ containing granulation tissue and atypical bone-cells.

PLATE 14



Epiphyseal junction in congenital syphilis; section stained with hematoxylin.

Associated Conditions.—Involvement of the neighboring parts is not infrequently seen in syphilitic diseases of the bones; thus there may be gummatous infiltration of the superficial tissues with syphilis of the bones of the extremities, while in the case of skull-bones extension inward may lead to involvement of the dura and brain. When the process occurs about the foramina of exit of nerves the sheaths of the latter may become involved. Gummata of the sternum sometimes lead to the formation of retrosternal collections of puriform material. Amyloid degeneration of various organs frequently follows bone-syphilis.

Actinomycosis

Actinomycosis attacks bones, most often those of the face and thorax. It occasions a rarefying, suppurative, or necrotizing complete osteitis, with involvement of adjacent tissues. There is little, if any, reactive limiting granulation tissue.

Lepra

Changes may occur in the bones in cases of mutilating leprosy, or more rarely in nervous lepra. Among these changes are ostitis and osteomyelitis associated with new tissue resembling lepra nodules; considerable destruction of the bones may be produced.

TUMORS

Exostoses are frequently met with in connection with definite disease of the bones and joints, or as more or less idiopathic outgrowths (see Fig. 55). They may be *cartilaginous* or *fibrous* in character, but subsequently may become *osseous*. They present themselves as flat, rounded elevations, or as more or less irregular outgrowths. Sometimes they are multiple and involve a number of bones of the skeleton. In such cases, particularly, heredity has been claimed as an important cause.

Similar hypertrophic growths may appear within the marrow canal, especially in spongy bone, *enostoses*.

Fibroma, lipoma, myxoma, and angioma may be mentioned among the true tumors as benign growths occasionally met with. They arise most frequently from the periosteum.

Chondroma and osteoma are more common than these, and involve any part of the bone (see Figs. 53 and 56, pp. 177, 180).

Sarcoma.—The most important of the primary tumors of bone is sarcoma. This may originate in the periosteum, bone-marrow, or the bone itself. It may be spindle-celled, or less frequently round-celled or alveolar. Sometimes it is melanotic. The giant-cell sarcoma, or osteosarcoma, is particularly important. It is most frequently met with in the lower jaw, beginning within the bone and causing a more or less rapid swelling. The tumor is surrounded by a shell of bone, which, however, sooner or later becomes perforated when the new

growth spreads to the neighboring parts (see Fig. 64). In all forms of sarcoma there is absorption of the bone substance in the vicinity. A form of sarcoma springing from the periosteum is described under the name of *osteoid sarcoma*. This tumor consists of fibromatous or round-celled sarcomatous tissue in which osteoid elements are irregularly embedded. More or less calcification and bone-formation are observed. The tumor may be quite soft or very hard; it tends to spread to the marrow cavity and absorb the shaft; it also extends to neighboring soft parts and may give rise to metastasis. It is particularly frequent at the ends of the long bones (see p. 196).

Sarcoma from the periosteum forms nodular swellings, while that arising within the bone gives a fusiform growth because of its tendency to spread lengthwise.

Secondary sarcoma of the bone-marrow is not rare in general sarcomatosis.

Myeloma.—This term has been applied to a form of multiple primary tumor of the bone-marrow allied to the lymphatic growths of leukemia. The term *lymphadenia ossea* has also been given to it. There are three types—the *myeloid*, in which myelocytes predominate; *lymphoid*, made up chiefly of small deeply staining cells, and the *plasma-cell type*. However, all these cells are represented in each tumor. The growths attack the shaft of the bones and fractures or bends may occur.

Chloroma is a form of sarcoma, having a greenish or yellowish color, that is met with in the periosteum, especially about the orbits and other parts of the skull.

Primary carcinoma of the bones has been observed in a few cases. It can only be explained upon the assumption that islets of epithelial tissue have been deposited in the bone by faulty development. Most cases, however, described as primary carcinoma were probably in reality alveolar sarcomata.

Secondary carcinoma of the bones is not rarely met with, especially in cases of cancer of the breast, thyroid gland, and prostate. The secondary nodules may occupy the periosteum or the bone-marrow. The bone becomes exceedingly fragile, and fractures are not infrequent.

Secondary tumors of bones are commonest as metastases from the breast, adrenal prostate, kidney, and thyroid, and involve most frequently ribs, vertebræ, femur, humerus, and cranium. Thyroid-tumor metastases are usually single.

Cysts and Parasites.—Cystic transformation of myxomata and of sarcomata may be met with. Occasionally, dermoid cysts are observed. Among the parasitic diseases *Cysticercus cellulosæ* has been described in a number of instances.

CHAPTER X

DISEASES OF THE JOINTS

Luxation.—The most frequent injury of joints is that known as luxation, in which the relations of articulating bones are disturbed. In these cases the ligaments and other soft tissues around the joints are more or less torn, and in consequence become inflamed. If the luxation is reduced, this inflammation subsides quickly, and frequently normal conditions are restored. If the luxation persists, various secondary changes may occur. Ankylosis in abnormal positions may take place by the formation of fibrous adhesions, or in more favorable cases a false joint may be established. In the latter cases local atrophy takes place in one of the bones, forming a depression into which the end of the other fits. Later, ossifying periostitis produces an elevation around the depression of the socket, and thus a well-formed joint may be produced. Luxation may be congenital, due to hypoplasia of the joint surfaces or their surrounding tissues.

Ankylosis is the term applied to the condition in which the normal movability between articulating bones is prevented by interosseous attachments. Pathologically, ankylosis may be *fibrous*, *cartilaginous*, or *bony*. All of these forms are met with after chronic inflammatory conditions of the joints. The ankylosis may be due to growing together of the joint surfaces by fibrous, cartilaginous, and bony deposits of the arthritis, or the fixation may be due to periarticular changes if the same pathological processes occur around the joint, as in arthritis deformans.

DISTORTIONS OF JOINTS

Distorted conditions of the joints may be due to congenital malformation, to contractions of the muscles and tendons, or to cicatricial tissue in the neighborhood of the articulation. Changes in the joints themselves may be present as primary or as secondary conditions. Among the more important of such deformities of joints are the various sorts of **club-foot**: *pes varus*, the sole of the foot turned in; *pes valgus*, the sole of the foot turned out; *pes equinus*, the foot extended and supported upon the anterior ends of the metatarsal bones; *pes calcaneus*, the foot flexed and resting on the heel. Combinations of these conditions are frequently met with. At the knee-joint are found: *genu valgum*, in which the knees are bent in (knock-knee), and *genu varum*, in which the knees are bent out (bow-legs).

CIRCULATORY DISTURBANCES

Hyperemia of the joints occurs as a part of acute inflammations, and involves the synovial membranes particularly. The synovial fluid may be increased in quantity.

Hemorrhage into the joint may result from traumatic causes or from inflammatory conditions, particularly in the course of hemorrhagic diseases, notably scurvy and hemophilia. The blood may remain fluid for a long time, and the joint not rarely has the appearance of chronic arthritis with effusion. Later, resorption of the blood takes place.

Dropsy of the joints occurs in the course of acute and chronic inflammations.

INFLAMMATIONS

Acute arthritis may be traumatic or due to hematogenous infection; in other cases it is secondary to disease in the vicinity. Hematogenous arthritis may occur in the course of various infectious diseases, such as scarlet fever, small-pox, pyemia, etc. In the same group must be considered acute articular rheumatism, which is doubtless an infection conveyed to the joint through the blood.

Pathological Anatomy.—Various grades may be distinguished, such as the *dry* or *fibrinous*, the *serous*, and the *purulent*. In all cases there is, first, a deep congestion, swelling, and infiltration of the synovial membrane. The ligaments and the cartilage are more or less implicated at the same time. The terms *synovitis*, implying involvement of the synovial membrane, and *panarthritis*, implying general involvement, may be applied. In the dry or fibrinous form there is a deposit of fibrin upon the surface, with or without serous exudation. In the genuine serous form the exudation is purely serous, but more commonly seropurulent liquid is observed. Entirely purulent exudate is sometimes formed (empyema of the joints). Acute inflammatory rheumatism is a serofibrinous arthritis.

Results.—In the milder cases complete resolution may take place without destruction of the tissues of the joint. In the more serious cases there is inflammation of the articulating cartilages, with consequent ulceration or caries, or even considerable necrosis, of the cartilage. The underlying bone may be laid bare, and osteitis or osteomyelitis may result. Sometimes discharge of purulent material into the surrounding tissues occurs, and fistulous communications with the exterior may be established. These processes may lead to extensive disorganization of the joints, with luxations and, in later stages, ankylosis.

Associated Conditions.—About joints the seat of acute inflammation there is always a peri-arthritis or, at least, an edematous swelling. General systemic infection may follow these acute inflammations of the joints.

Chronic arthritis may be due to a variety of causes. It may follow the acute forms already described or may be primarily chronic. Among

the more important causes are traumatism and certain infections. It occurs in the course of gout and in certain nervous diseases, probably as the result of disturbance of the trophic mechanism. Chronic arthritis of the aged and arthritis deformans are allied forms of joint disease, probably infectious or toxic in many cases. Other factors, such as nervous or trophic disturbances, may play a part in the etiology in some cases.

Pathological Anatomy.—A variety of forms may be distinguished. The same etiological factors may, however, give rise to one or another in individual cases.

Chronic serous arthritis, or hydrops articularum, is frequently due to repeated acute arthritis. The joint is filled with thin synovia, and the synovial membrane is somewhat thickened. The surface of the joint may be more or less covered with an injected synovial membrane (*synovitis pannosa*). The knee-joint is most frequently involved.

Chronic purulent arthritis is always infectious, and is usually the outcome of an acute seropurulent or purulent arthritis. The conditions met with have already been described. It terminates in more or less extensive disorganization of the joint, and in favorable cases in fibrous ankylosis (Fig. 412).

Occasionally, one sees a combination of the two preceding forms with tendency to scanty exudate, ulceration of the cartilages, and early formation of connective tissue. This is the so-called ulcerative adhesive chronic arthritis.

Arthritis Deformans.—This term may be used to include a group of conditions probably of varied etiology characterized by certain deforming changes in the tissues constituting joints, and to an extent also in the adjacent bones and ligaments.

The cartilages entering into the articulation atrophy, and may either be uniformly thinned or irregularly indented or furrowed. The articular surface may be extremely roughened and irregular. Later, or simultaneously, the edges of the cartilages may present hypertrophic changes. Usually, this takes the form of "lipping" or projecting ecchondroses at the sides of the joint, sometimes of considerable magnitude. Similar hyperplastic cartilaginous change may occur on the articular surface or in the synovial tissues, and the ligaments about the joint.

The bone beneath the articular cartilages or where it has been exposed by atrophy or erosion of cartilage becomes more or less sclerosed (eburnated), or may suffer an atrophic process. Secondary ossification of ecchondroses and of the cartilaginous transformations of the soft



Fig. 412.—Fibrous ankylosis, due to chronic purulent arthritis.

tissues is sometimes present, and especially in the spine leads to pronounced disability.

The synovial membrane and the ligaments about the joints are usually affected, and in some cases are the chief seats of alteration. Thickening and fibrosis may occasion considerable fibrous ankylosis. In some cases villous outgrowths from the synovial membrane are abundant, and these may become cartilaginous and may be separated as free bodies within the joint.

Clinical Types.—(a) Arthritis deformans in its most familiar form is polyarticular and affects the small joints of the hands and feet primarily. Later, though often simultaneously or even before the small joints are



Fig. 413.—Arthritis deformans, showing extensive deformity of the hands.

involved, the knees, elbows, and other large joints suffer a similar change. This form is most frequently encountered after the third decade of life, but may occur in younger persons and even in childhood. The disease is insidious in onset and progressive up to the most advanced deformity.

(b) In other cases a more acute onset and more active evidences of joint inflammation cause a nearer clinical resemblance to articular rheumatism. This form also is usually polyarticular and has practically the same distribution as the first type. In the end the joint changes may be identical, but not infrequently fibrous tissue growth remains predominant in this type. The suggestion of an infection is most pronounced in this group. A class of cases, described by Still as occur-

ring in young children and associated with glandular and splenic enlargement, anemia, and fever, should perhaps be included here.

(c) Senile arthritis of the hip (*malum coxæ senile*) and the similar types of *dry arthritis* of the knee and other joints, in which moderate cartilaginous erosion and absorption, and atrophic or hyperplastic changes in the ends of the bones occur, constitute another group.

(d) **Heberden's nodes** are bony enlargements at the sides of the terminal interphalangeal joints of the fingers. These may occur independently or in association with other joint changes. The process is similar to that seen in other types.

(e) **Spondylitis deformans** is a deforming and ossifying type of arthritis of the spine. In some cases the intervertebral disks become atrophic and bony ankylosis takes place between the bodies of adjacent vertebræ. In other cases bony ankylosis of the smaller articulations of the spine and ossification of the ligaments is the initial process. The spine may be rigid and straight, or may be markedly kyphotic. Sometimes the hips and shoulders and the articulations of the ribs may be involved.

Nomenclature and Etiology.—The general term *arthritis deformans* is preferred as sufficiently descriptive, and because it involves no theory regarding the precise type of pathological change or of etiology. The old name *rheumatoid arthritis* is objectionable because of the implied relationship with rheumatism. *Osteo-arthritis*, *atrophic arthritis*, and *hypertrophic arthritis* are terms properly used in some instances, but not definitely applicable as separating distinct types.

The etiology of the forms of joint disease, here included under one general term, may be very varied. Formerly, the occurrence of the common polyarticular form in persons who had endured hardships, exposure, or various kinds of physical and nervous depression, and the associated trophic changes in the skin and muscular tissues suggested a nutritional disorder or some nervous condition as the important etiological factor. In recent years attention has been drawn more and more insistently to the probability of infection or infectious toxemia. Hidden sources of infection (tonsils, teeth, nasal sinuses, gastro-intestinal tract) have been discovered in some cases, but not in all. Traumatism undoubtedly plays a part in initiating the disturbance in some cases.



Fig. 414.—Neuropathic arthritis of the knee in a case of locomotor ataxia (case of Dr. C. W. Burr).

Neuropathic arthritis is met with in the course of spinal diseases, such as locomotor ataxia and syringomyelia (Fig. 414). It resembles the forms just described, is slowly developed, and is usually quite painless, suggesting a purely degenerative or trophic disorder. In the early stages there is a large amount of exudate, which collects quickly. The absorption of the ends of the bone is more marked than in arthritis deformans.

Gouty Arthritis.—Gout is a constitutional disease with a tendency to a peculiar form of arthritis. The latter consists in the deposit of crystals of urate of sodium and calcium in the cartilage cells and intercellular substance of the articulations, and in more advanced cases in the connective tissue of the joints and the tissues round the joints (Fig. 415). These crystalline deposits occur in definite attacks,



Fig. 415.—Deposit of crystals of urate of sodium in an articular cartilage (Lancereaux).

as a rule, each attack (*gouty paroxysm*) being marked by inflammatory processes in the joint. Hyperemia of the synovial membrane, with serous effusions and with sometimes more evident inflammatory manifestations (hyperplasia of the cartilage cells and round-cell infiltration), is observed during the paroxysms, and by their repetition chronic changes in the joint are produced. The cartilages may become more or less eroded, and even

carious changes and suppuration may take place. The joints most frequently involved are the small joints of the hands and feet, notably the metatarsophalangeal joint of the great toe. The larger articulations are less commonly involved, and usually after the smaller joints.

Associated Conditions.—The pathology of gout is by no means confined to the changes in the joints. The disease is a general one, and pathological changes are found in various organs. There is a tendency to thickening of the blood-vessels, to atheroma, and to sclerotic changes in the kidney, liver, and heart; and uratic deposits may occur in the organs named or in the subcutaneous tissue or superficial cartilages, such as those of the ear and nose (*gouty tophi*). Concretions or calculi are frequently formed in the kidney or bladder.

INFECTIOUS DISEASES

Tuberculosis

Tuberculosis, when primary in the joints, usually begins in the synovial membrane. Occasionally, it arises by extension from lesions in the soft parts of the immediate vicinity or, more commonly, it is secondary to tuberculosis of the adjacent bone, from which source any part of the joint may be first involved.

PLATE 15



Gouty arthritis with urate deposits.



Gouty tophi in ear.

Etiology.—Tuberculous arthritis is most frequent in childhood, and occurs in those predisposed by heredity. The immediate determining cause may be traumatism, this serving to localize the disease in a joint rendered peculiarly susceptible. Lesions in the spongy bone, the result of vascular disease, seem to precede joint tuberculosis in many cases; the course as outlined under bone tuberculosis is undoubtedly the most frequent path of infection.¹ Tuberculous arthritis is frequently secondary to scrofulous disease of the skin or glands, or to pulmonary tuberculosis, but is often primary in the joint or adjacent bone ends.

Pathological Anatomy.—The changes met with in the joints vary somewhat in different cases. In instances beginning in the synovial membrane there are formed more or less abundant, soft, spongy granulations, which may eventually fill the entire joint cavity. These are pinkish or whitish in color, and may show gray or yellow spots or tubercles quite plainly. Later, this granulation tissue tends to degenerate, becoming mucoid or breaking down by suppurative or cheesy change. In the early stages the soft tissues of the joint are considerably inflamed and edematous; later, they may show ulcerative or necrotic change, and similar alteration may occur in the articular cartilages. Puriform softening of the granulations and the tissues of the joint may lead to the development of *cold abscesses* within the joint, and the latter may eventually burrow to the exterior. In cases progressing unfavorably the joint is greatly disorganized by the advancing necrotic changes. The abnormal productions are either discharged or inspissated, and ankylosis of the joint by fibrous adhesions takes place.

The external appearances of tuberculous joints are often quite distinctive. The joint is swollen and boggy ("white swelling") or somewhat elastic to the touch, and usually more or less distorted from subluxation. There is little evidence of acute inflammation. In cases terminating in ankylosis the bones are generally left in faulty position in consequence of the formation of adhesions and the irregular contractions of muscles.

Secondary Disorders.—Long-standing tuberculosis of the joints occasions profound disturbances of the general health and sometimes causes definite disease, such as amyloid degeneration of various organs. Disseminated tuberculosis rarely results.

Syphilis

Syphilitic disease of the joints may occur in hereditary lues. The cartilages of the joints are eroded, and thickening of the ligaments with puriform exudation into the joint is observed. The phalangeal articulations are most frequently involved. In later life gummata in the neighborhood of the joints may invade the latter by contiguity.

¹ The cases arising by primary involvement of the synovial fringes are often rather acutely inflammatory in character with a serous exudate, while those cases which extend from the ends of the bones are more protracted in their course, and are usually accompanied by rarefying or sclerosing osteitis about the tuberculous lesion.

TUMORS

Hyperplastic conditions are met with in the synovial fringes of the joints in association with arthritis or independent of such. These hyperplasias may take the form of *fibrous growths*, or they may become *lipomatous*. An interesting form of new growth is seen in the so-called rice-bodies or "joint-mice." These are small fibrous or cartilaginous bodies, up to the size of a small nut, which are entirely free in the joint or attached by a fine pedicle to the synovial membrane. They are formed from the synovial fringes, and probably result from injury or hypertrophic inflammation in most cases. They may be remains of blood-clots or broken-off polypoid hyperplastic synovial membranes. Occasionally, they undergo calcareous change. The joints may be secondarily involved in various forms of bony tumors.

THE TENDON-SHEATHS AND BURSAE

Inflammations of the sheaths of tendons (*tenosynovitis*) and of the bursae (*bursitis*) occur under similar circumstances and in similar forms as inflammations of the joints. A form of chronic bursitis with dropsical effusion frequently occurs in the bursa beneath the patella from chronic irritation (housemaid's knee), and in the bursa at the joint of the elbow (miner's elbow). These conditions are analogous to *hydrops articulorum*. Gout gives urate deposits in the tendons, their sheaths and bursae, with considerable exudate or infiltration or even-necrosis.

Ganglion is a condition of the tendon-sheaths of some clinical interest. It presents itself as a rounded cystic nodule, most frequently upon the back of the hands and wrists. Distinct fluctuation may be discovered, or the cyst may be so dense that it feels stony hard. The ganglion results from a localized dropsical condition of the sheath of the tendons, with frequently a lateral hernious projection. A similar condition is sometimes caused by projection of the synovial membrane of the joints. This condition is sometimes tuberculous, occasionally primary in a clinical sense, at other times secondary to bone tuberculosis. This form contains rice-bodies.

Tumors are rare, but a so-called myeloma, which seems more like an endothelioma, has been reported.

CHAPTER XI

DISEASES OF THE VOLUNTARY MUSCLES

Congenital malformations are occasionally met with, such as absence of a part or of an entire muscle.

HYPERTROPHY

Hypertrophy is frequently produced by athletic exercise or laborious occupations. This affects the parts brought into play, and is proportioned to the amount of work and the constitution or condition of the individual. The muscle-fibers increase in thickness and probably also in number.

Sometimes muscular hypertrophy is met with in cases in which no adequate cause is discoverable. Thus in local or general giant growths the muscles may be involved with other parts.

Pseudohypertrophy will be discussed among the degenerative conditions.

CIRCULATORY DISTURBANCES

Anemia of the muscles may be part of a local or general anemia; it is often quite insignificant in comparison with anemia of other parts. In some of the general anemias the muscles may present a dark appearance, due to degenerative conditions.

Hyperemia is physiological during and after exercise. It occurs as an active process in association with inflammatory conditions and as a passive congestion in cases of vascular stasis.

Hemorrhages may be traumatic, or may result from rupture of the vessels in consequence of inordinate blood-pressure or local degeneration of the vessel walls and the surrounding muscle-fibers. Among the conditions in which hemorrhage takes place are tetanus and other convulsive disorders, fevers, and hemorrhagic diseases such as scurvy or hemophilia, and septic diseases. The hemorrhages may occur in the form of small extravasations between the fibers, or of more extensive infiltrations in the intermuscular planes. In cases of traumatism, scurvy, or hemophilia, considerable blood-tumors may be formed, the muscle-fibers being pushed aside or torn apart. The blood is more or less rapidly absorbed. Pigmentation and fibrous-tissue proliferation may result.

Embolism of the arteries or **thrombosis** of the veins does not produce serious disturbances, as a rule. In cases of embolism, secondary results may follow if the embolism is infective.

INFLAMMATIONS

Inflammation of the muscles, or myositis, may be acute or chronic, and may present itself in a variety of forms. Acute myositis may be local or disseminated.

Localized Acute Myositis.—This form may be due to injuries, such as contusions of the muscles or wounds communicating with them, or may be infectious in character, resulting from the direct extension of infectious diseases of the skin, subcutaneous tissues, bones, and other adjacent parts, or from embolism. A serous, a hemorrhagic, and a purulent form may be distinguished.

Serous myositis is characterized by an edematous condition of the muscle, which gives it a peculiar gelatinous appearance on section. Microscopically there is cellular infiltration of the muscle-bundles, while the muscle-fibers themselves become swollen and suffer granular degeneration or hyaline change, and sometimes vacuolation.

Hemorrhagic myositis is an intense form, and is met with in muscles adjacent to gangrenous or phlegmonous lesions, malignant pustules, and the like. Myositis occurring in scorbutic individuals is frequently of the hemorrhagic form, as is also that which occurs in consequence of the sting of venomous snakes or other animals. The muscle becomes more or less tensely swollen, and on section the hemorrhagic infiltration is plainly visible as a diffuse process or as localized areas of hemorrhage.

Suppurative myositis may be circumscribed or diffuse. Circumscribed myositis, or abscess of the muscle, may result from entrance of micro-organisms through the lymphatic or vascular circulation, or it may be due to traumatism, with communications from the surface. Occasionally suppurative inflammation occurs in an obscure manner, when the term cryptogenetic myositis is applicable. Distinctly metastatic abscesses may be occasioned by embolism.

In association with suppurative inflammations of the skin or subcutaneous tissues and the mucous membranes there may be seropurulent or phlegmonous myositis, with the formation of irregular abscesses. In these cases the lesion spreads by infiltration, and the muscle-fibers undergo widespread degeneration (fatty degeneration, hyaline change, and necrosis). Abscesses in the muscles extend and rupture in various directions, and may leave considerable areas of scar-formation.

Disseminated acute myositis or polymyositis may appear without any definite cause, sometimes in association with tuberculosis of the lungs, or as a distinctly secondary affection in association with infectious diseases, like typhoid fever, diphtheria, etc. In the primary form there may be widespread muscular disease, with swelling and tenderness of the muscles and sometimes redness and edema of the skin. The term *pseudotrachinosis* was applied from the resemblance of the appearances to those of trichinosis, and the name *dermatomyositis* has also been given this condition. In several cases this disease has been shown to be a bacteremia due to a form of *Staphylococcus pyogenes*, the organism

having a predilection for the muscles, as indicated by animal experimentation. Some of the conditions included under the heading *muscular rheumatism* by clinicians are doubtless instances of the kind here discussed. Examination of the muscles shows pallor of the tissue and sometimes visible areas of degeneration. Microscopically there are cellular infiltration between the muscle-fibers and swelling, with loss of striation of the fibers themselves. More advanced degenerations of the fibers, such as granular change, coagulation-necrosis, and vacuolation, may be observed. The affected muscles lose their functional contractile power, and more or less palsy results. When affecting the muscles of the pharynx and respiration this becomes serious in predisposing to inspiration pneumonias.

The condition described as secondary acute polymyositis is degenerative to a greater extent than inflammatory, and will be considered among the degenerations.

Chronic myositis may be suppurative in type or productive.

Chronic suppurative myositis may be the outcome of acute supuration, and is particularly frequent in association with tuberculosis and actinomycosis.

Chronic productive myositis is characterized by the formation of connective tissue between the muscle-fibers. The fibers themselves, as a rule, undergo degenerative changes, though occasionally showing regeneration to some extent. This condition may be the termination of acute myositis, or it may occur in the vicinity of various localized diseases of the muscles or of the neighboring parts. In some cases, if not all, the primary change is degeneration of the muscle-fibers, and the interstitial or fibrous tissue is reactive in character. Some of the cases will be considered under the head of muscular atrophies. The changes that occur in the interstitial tissue of the muscles consist primarily of proliferation and round-celled infiltration. Later, there is formation of firm connective tissue. Some multiplication of the muscle-nuclei and actual increase in size of some muscle-fibers may be observed. Degeneration of the muscle-fibers, however, is more prominent, and is generally in proportion to the degree of connective-tissue change. The fibers may show cloudy swelling or hyaline changes, or more complete degeneration, such as fatty degeneration, fragmentation, or vacuole formation.

Ossifying myositis is a variety of productive myositis. It may occur in the form of bony nodules in parts subjected to constant irritation or strain, as in the case of the deltoid muscle in soldiers and the adductor muscles in horsemen. Similarly, in the vicinity of disease of the bones and periosteum, nodules may develop in the muscle. A form of more general disease, termed *myositis ossificans progressiva*, has been observed in youthful persons, without discoverable cause. It affects the muscles of the back and neck, and sometimes those of all parts of the body. The muscles are swollen, and first present inflammatory manifestations, terminating in fibrous change which finally leads to bone-formation. The osseous tissue is at first in the form of spicules or

small nodules, but gradually increases to considerable proportions. The muscles themselves contract, and various deformities with pseudo-ankyloses may result. The muscles of the face, diaphragm, and heart are unaffected. A peculiar malformation has been found associated with 75 per cent. of the cases. This is a form of microdactylism—ankylosis of the phalanges of the thumb and lack of one phalanx of the great toe on both sides.

ATROPHY AND DEGENERATIONS

Several forms of atrophy are recognized. Certain cases are dependent upon disease of the spinal cord or nerves (neuropathic form), others occur as primary diseases of muscles (myopathic form), and in another group the change is due to simple nutritional processes (simple and senile forms).

Neuropathic muscular atrophy may be the result of disease of the anterior horns of the gray matter of the cord or of neuritis. To the cases in which this lesion is the underlying pathological condition the



Fig. 416.—Neuropathic muscular atrophy, showing atrophy of the muscle-fibers, increase in the interfascicular fibrous tissue, and thickening of the blood-vessel walls.

term *progressive muscular atrophy* has been applied. The causes of this disease are obscure.

It leads to progressive atrophy of the muscles of the hands, arms, and shoulders, and less frequently of those of the body and buttocks. It usually begins in the small muscles of the hands, but sometimes affects those of the shoulders first. The muscles become pale and rather flabby. Microscopically, the fibers show various forms of degeneration. Fragmentation in a longitudinal or in a transverse direction, coagulation-necrosis, and occasionally fatty degeneration of the fibers may be seen. Sometimes the fibers seem to grow smaller by a simple atrophic process (Fig. 416). Coincidentally, reactive proliferation is seen in the connective tissue between fibers, and doubtless this to some extent

causes further muscular degeneration. The muscle-cells themselves may proliferate quite extensively.

Secondary neuropathic muscular atrophies may occur in various spinal diseases, such as syringomyelia and in degenerations following cerebral disease. These are essentially similar in character to the primary neuropathic variety, though their clinical character is different. Section, disease, or injury of motor nerves may lead to local atrophies by separating the muscles from their trophic centers in the cord.

Myopathic muscular atrophy occurs in children and young persons, and is frequently hereditary. It begins in the buttocks, thighs, or calves, and sometimes in the shoulders. Two forms have been distinguished: the simple atrophic form and the pseudohypertrophic form. The anatomical changes in the former are the same as in the neuropathic variety just described.

Pseudohypertrophic Muscular Atrophy.—In this condition the muscles increase greatly in size, but are soft and flabby. The child may present the appearance of an athlete, with enormous calves and thighs, but is extremely weak and can scarcely stand. Microscopically, the causation of the enlargement is found to be a considerable degree of intermuscular proliferation of connective tissue, with marked fatty infiltration. Sometimes in this form, as well as in other varieties, some actual enlargement of the muscle-fibers is observed, but this is doubtless degenerative.

To this group probably belongs the *myotonia congenita* of Thomsen. In this form some fibers are definitely hypertrophic, but the general muscular mass is atrophic. A suggestion of hyperplasia is given by increase of nuclei, but this may arise from fiber splitting.

Simple muscular atrophy may be senile in origin or due to lack of exercise. In these cases the muscle-fibers become smaller, and some proliferation of the connective tissue is generally present. In senile cases brown atrophy may occur, brownish pigment particles being deposited in the atrophic fibers, especially near the nuclei.

Parenchymatous degeneration of the muscles may occur in the vicinity of inflammatory lesions, tumors, or other areas of disease. It may also occur in the course of infectious diseases in association with coagulation-necrosis. The fibers become cloudy and lose their striated appearance from the presence of minute granules. In some instances inflammatory changes in the interfascicular connective tissues are associated with the degeneration of the fibers. Cases of this sort may be called *secondary acute polymyositis*.

Fatty degeneration is found under the same circumstances as the above, and also in chronic cachectic diseases and in cases of poisoning with phosphorus and other "parenchyma poisons." The muscle-fibers have a streaked or spotted, yellowish appearance, and are more or less flabby. Microscopically, the fibers are seen to be filled with small oil-droplets which obscure the striations. All parts of the fiber may become degenerated until the sarcolemma sheath contains only a mass of fat-droplets and detritus (Fig. 418).

Fatty infiltration may occur in association with atrophy in the condition above described—pseudohypertrophic muscular atrophy; and in various nervous diseases in which the muscles waste from disease or trophic change. A certain amount of lipomatosis may occur in general obesity. This fat increase also occurs in cases of abnormal carbohydrate metabolism.

Amyloid degeneration is rare and unimportant.

Calcification may occur in the form of ossifying myositis, and locally in scars following various local diseases—abscesses, etc.

Coagulation-necrosis, or hyaline degeneration, is of great clinical importance. It was first discovered by Zenker as one of the lesions occurring in typhoid fever. The muscle-fibers at first become granular and cloudy (*parenchymatous*

Fig. 417.—Muscle from a case of carcinoma of the esophagus, showing the presence of fat and pigment at the ends of the nuclei. From a drawing. $\times 1000$. (Jewesbury and Topley, in Journal of Pathology and Bacteriology.)

degeneration), and later waxy or hyaline change occurs in streaks or completely transform the fibers. Transverse fragmentation is common,

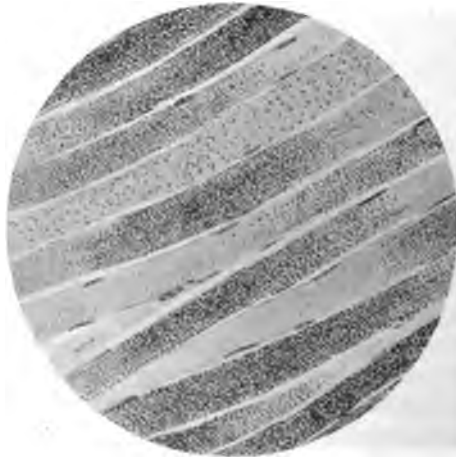


Fig. 418.—Section from a case of infective purpura, showing well-marked true fatty degeneration. From a drawing. $\times 450$. (Jewesbury and Topley, in Journal of Pathology and Bacteriology.)

and gross rupture of the muscle may be found. In the latter cases hemorrhagic infiltration, or even considerable hemorrhage (*hematoma*).

may be occasioned. Reactive inflammatory change in the interstitial connective tissue is generally present. This disease occurs in the course of typhoid fever, but also in various other febrile and infectious conditions. It is most common in the abdominal muscles (rectus abdominis), in certain muscles of the extremities, and in the heart. The latter situation is, of course, of greatest significance. (See Diseases of the Heart.)

INFECTIOUS DISEASES

Tuberculosis may occur in the form of cold abscesses in association with tuberculous disease of bone or less frequently of the lymphatic glands or other parts. In these cases there is a gradual extension of the caseous and liquefying tuberculous disease into the muscles, and sometimes the abscesses burrow to great distances within the muscular sheath, as, for example, in *psoas abscess*. Less destructive tuberculous myositis may occur in the muscles beneath the skin and mucous membranes by extension of tuberculous processes. In these cases cellular infiltration and tubercle formation, with some caseous change, may be observed. Miliary tubercles, or larger tuberculous nodules due to hematogenous infection, are rare.

Syphilis may occur in the form of gummata, and it is likely that some cases of diffuse productive myositis are syphilitic in nature. As in other parts of the body, the blood-vessels in these cases have been described as particularly thickened.

Glanders, actinomycosis, and anthrax may involve the muscles in the vicinity of the specific lesions. Nodular and, later, necrotic or suppurative foci are the lesions observed.

TUMORS AND PARASITES

The tumors of muscles, for the most part, spring from the interstitial connective tissue. Among the benign tumors *fibromata*, *myxomata*, and *lipomata* are sometimes met with. *Osteoma* and *chondroma* are found as localized lesions resulting from irritation or as true tumors. Striped muscle tumors, or *rhabdomyomata*, are rarely found in the muscles, though occasionally seen as small nodules.

More important than the above is *sarcoma*, which occurs as a primary tumor comparatively frequently. The fibrous and spindle-celled varieties are common, and round-celled sarcoma are sometimes observed. The tumors originate from the connective tissue, though it is held by some that the muscle-fibers themselves may undergo sarcomatous transformation.

Carcinoma is a rare tumor, and is always secondary. The secondary form is not rarely seen in the muscles in the vicinity of carcinomata of other structures, such as the mammary gland.

Among the *parasitic diseases* of muscles may be mentioned trichinosis, cysticercus invasion, and hydatid disease. The first occasions disseminated myositis, to which reference has already been made. The other two conditions are rare and not important.

CHAPTER XII

DISEASES OF THE BRAIN AND ITS MEMBRANES

THE DURA MATER

THE dura mater forms the inner covering of the skull and acts as a firm support of the brain. It consists of dense connective tissue; and is poor in blood-vessels, but reflections of the membrane surround large venous sinuses.

CIRCULATORY DISTURBANCES

Active hyperemia occurs in the dura in association with tumors, gummata, and other focal diseases. The vessels of the dura surrounding the area of disease become distended and the membrane may be diffusely reddened.

Passive hyperemia may occur under the same circumstances as the above, and also in cases of thrombosis of the venous sinuses.

Hemorrhages are usually due to traumatism, and may occur on the outer or inner surface of the dura. Extradural hemorrhages are more common than intradural, especially in cases in which there is fracture of the skull. The blood in these cases comes from the skull bones and the vessels on the outside of the dura. It does not collect quickly, and tends to gravitate to dependent parts. It exerts pressure by its bulk, and may cause cerebral degeneration beneath it. A collection of blood between the skull and the dura is sometimes designated *internal cephalohematoma*. Small hemorrhages into the dura may occur in infectious or hemorrhagic diseases and in cases of death from asphyxia.

Sinus Thrombosis.—This condition, like other thromboses, is due to altered blood or vessel states, or to inflammation, of which the last is most important. Traumatism and infections are the commonest causes; the former usually produces the formation of a clot in the longitudinal sinus, while the lateral sinus is most often involved by extension of infections from the mastoid cells. Infective thrombi are prone to lead to septicopyemia. Surrounding parts are at first edematous, then inflamed. The clot is usually soft and necrotic, but may be laminated. Thrombi in the dural sinuses have a peculiar tendency to spread rapidly by extension.

INFLAMMATIONS

Inflammation of the dura, or pachymeningitis, may be acute or chronic, and hemorrhagic, suppurative, or productive in character.

Internal hemorrhagic pachymeningitis occurs more frequently in the aged than in the young, and is not uncommon in the insane. Chronic

alcoholism and traumatism seem to be etiological factors of some importance. In the early stages of the disease the *inner* surface of the dura exhibits a superficial deposit or membrane of grayish color, with brown or red spots, the former being composed of altered blood-pigment (hematoidin). Often several layers are present, indicating successive exacerbations. Microscopically, the membranous deposit is found to consist of soft granulation tissue containing numerous thin-walled blood-vessels. Later, diapedesis of blood-corpuscles, or actual hemorrhages, occur, and the diseased area may have the appearances of a simple collection of blood or of a more or less stratified hemorrhagic exudate. Sometimes the amount of exudate and of hemorrhage may



Fig. 419.—Nodular tuberculous pachymeningitis. The mass to the left is the product of the chronic change in the dura and fitted into the depression in the hemisphere (from a specimen in the collection of Dr. Allen J. Smith).

be such as to cause considerable cerebral compression, and in other cases death may occur from the hemorrhage itself. Occasionally the blood is in part absorbed, and a serous collection (*hydroma duræ matris*) results. The seat of the disease is usually in the area of distribution of the middle meningeal artery. The process is slow, and recurs or is continued by irritation of the granulation tissue. The dura grows internally by diffuse or localized thickening, but rarely adheres to the pia arachnoid.

Suppurative external pachymeningitis may occur in consequence of injuries, caries, or other diseases of the skull. Sometimes it results from purulent softening of thrombi in the venous sinuses, and very

rarely it is secondary to leptomeningitis. Not rarely localized suppurative pachymeningitis results from disease of the middle or internal ear, with extension through the petrous bone. The dura becomes thickened by cellular infiltration, is soft and edematous, and not rarely undergoes necrotic change. The disease may be localized or diffuse, and may occasion secondary thickening and adhesions of the dura in cases terminating favorably.

Productive pachymeningitis may be of fibrous or ossifying character. The etiology is often obscure. Some cases follow hemorrhagic or suppurative pachymeningitis; in others the process seems to be primarily productive. Traumatism may cause proliferation of fibrous tissue in the dura. This is especially apt to occur after fractures of the skull in children, when, as a result of its adhesion to the bone, the dura is almost invariably torn. Syphilis is probably a cause of importance. The dura, in the fibrous variety, is simply thickened and more or less attached to the pia-arachnoid and the inner surface of the skull. When firm attachments with the skull are formed, osteophytes are frequently found upon the surface of the bones and in the dura (ossifying pachymeningitis). Osseous plates may be met with in the falx cerebri and tentorium cerebelli.

INFECTIOUS DISEASES

Tuberculosis may occur in the form of miliary tubercles in association with tuberculous leptomeningitis. It may also be associated with tuberculosis of the bones; and, in rare instances, has been met with as a primary disease of the dura. In the latter cases the disease takes the form of a caseous nodular thickening of the membrane (Fig. 419).

Syphilis may occasion a form of diffuse productive pachymeningitis, or gummata. The latter may originate in the dura and extend to the pia or skull bones, or they may originate in the bones and invade the dura secondarily. Gummata in this situation present themselves as more or less flattened nodular growths of grayish color, having a marked tendency to caseous change and to resolution, with formation of circumscribed thickenings and adhesions of the dura.

TUMORS

Tumors of the dura mater occur with considerable frequency. Among the pathologically benign growths are fibroma, osteoma, and chondroma. The most common tumor is probably some form of sarcoma. The *alveolar* variety may occur in various situations, either as a flat swelling or as a somewhat pyramidal mass, with the apex toward the brain, into the substance of which it projects; it is often firmly attached to the skull. Other forms of sarcoma are *angiosarcoma* and the *small round-cell variety*, which is usually multiple and the result of metastasis from some other part. The latter tumors are usually flat, diffuse, and often extensive. They may or may not cause bulging of the skull.

Statistical studies have shown that *endotheliomata* are among the most common tumors in this region. They usually occur as single irregular masses; but occasionally they are multiple, and it is possible that in these cases metastasis has occurred. Ordinarily they produce no disturbances in the brain, but in some instances pressure-symptoms have been reported. In any of these forms, but particularly in those in which the fibrous connective tissue is in excess, calcareous infiltration is not uncommon (*psammoma*). In nearly all cases these tumors produce erosion of the inner surface of the skull. Hyaline degeneration of the intercellular substance is very common.

Among the other tumor-like growths are fibrous changes that may or may not be inflammatory in nature, and lead to circumscribed or diffuse thickening of the dura mater, and usually cause it to adhere densely to the skull. These are most apt to be found in old people. In addition to the round-cell sarcoma, *gliosarcoma* of the brain and *carcinoma* of the scalp may give rise to secondary growths in the dura mater, but these are extremely rare.

CYSTS

Cysts of the dura are usually due to its protrusion through the skull and the escape of cerebrospinal fluid into the protruded portions. This is spoken of as *meningocele*. Two varieties are recognized, true and false. True meningocele is produced by the bulging of the dura mater through some congenital fissure in the skull. It is difficult to distinguish this from encephalocele (*q. v.*). False or spurious meningocele is almost invariably the result of some injury before the third year of life, such as fracture of the skull and effusion of blood. Later the blood is absorbed and replaced by a clear fluid, leaving only a brownish layer upon the inner surface of the cyst. As in early life the dura is adherent to the skull, it is usually torn at the time of fracture; and ordinarily there is also a laceration of the arachnoid, allowing the escape of the cerebrospinal fluid into the sac, which is formed externally chiefly by the pericranium. As a result of pressure, of bone absorption, or of defective growth, the opening in the skull usually enlarges considerably, and ultimately there is extreme deformity of the head. In cases where the brain has been lacerated at the time of injury, porencephalic cavities may occur, which in some instances have communicated with the lateral ventricles. The commonest situation for these cysts is the parietal bone; but they may occur in the frontal or occipital regions, and in rare cases are multiple.

THE PIA-ARACHNOID

This composite tissue consists of two layers anatomically, but because of their close physical and physiological relations are to be considered as one membrane. The outer layer, the arachnoid, consists of loose connective tissue full of spaces continuous with the perivascular

channels of the pia; in these spaces is a limpid fluid, the cerebrospinal fluid. The pia follows the convolutions of the brain very closely, and there is intercommunication of the vessels of this covering and of the choroid plexus. From these facts it is easy to see how infections of the pia-arachnoid may extend inward.

CIRCULATORY DISTURBANCES

Anemia of the pia may occur in cases of general anemia.

Active hyperemia is constantly present in the early stages of meningitis. It is also met with in cases of death from alcoholism and in severe infectious fevers, though in most of these cases microscopical examination discloses the fact that the process is really one of beginning inflammation. The pia is red and the small arterioles are injected. The fluid in the subarachnoid space is in excess, and may be slightly turbid or sanguinolent.

Passive hyperemia occurs in cases of general venous stasis, as in heart disease, pulmonary disease, and venous thrombosis. The large veins are greatly swollen, and the subarachnoid fluid is excessive.

Hemorrhages.—Small punctate hemorrhages may occur in cases of meningitis, in scurvy, purpura, and the like. Larger hemorrhages between the pia and arachnoid are most commonly due to traumatism, and may sometimes be the result of rupture of aneurysms. Punctate hemorrhages are said to occur during severe infections and upon absorption to leave small opaque areas in the pia; such white spots are indeed frequently seen at autopsy. The blood in cases of large hemorrhages may cause injurious cerebral compression, if death does not follow the injury itself. Occasionally the blood becomes inspissated and absorbed, the membranes in these instances becoming thickened and pigmented, or it may be encapsulated and the pigment absorbed, giving rise to a clear cyst (*hygroma*).

Edema of the membranes, or collections of liquid in the subarachnoid space (external hydrocephalus) may be due to passive congestion. The membranes are thickened and of a translucent or gelatinous appearance; the subarachnoid fluid causes elevation of the arachnoid and more or less compression of the cerebral convolutions. *Hydrops ex vacuo* is a form of dropsical effusion under the arachnoid, resulting from atrophy or hypoplasia of the cerebral convolutions. The space normally occupied by cerebral substance is in these cases filled with cerebrospinal liquid.

INFLAMMATION

Inflammation of the arachnoid and pia is called **leptomeningitis**. It is always an infectious process, and may be either acute or chronic.

Etiology.—The commonest cause of sporadic acute leptomeningitis is the pneumococcus. It is found in about 60 per cent. of all cases, and in these pneumonia is often an associated or primary condition. The

pneumococcus may reach the meninges either by the blood- or lymph-channels, or by creeping along the lymphatic spaces in the areolar tissue between the esophagus and vertebral column; occasionally it enters directly from the ear or nasal cavity. Other micro-organisms that have been found are the streptococcus, the staphylococcus, Friedländer's bacillus, the *Bacillus pyocyaneus*, the bacillus of glanders, the influenza bacillus, the actinomyces, the typhoid bacillus (of which a number of cases have been reported), the *Bacillus coli communis*, and the bacillus of bubonic plague. Meningitis occasionally occurs in the course of gonorrhea in which the gonococcus is probably the bacterial cause, although this has been questioned. Mixed infection is not uncommon, consisting usually of the pneumococcus and one or other of the more common pyogenic micro-organisms, and the latter are also



Fig. 420.—Leptomeningitis purulenta cerebri (Karg and Schmorl).

frequently found associated with the tubercle bacillus. The cause of epidemic cerebrospinal meningitis is the *Diplococcus intracellularis meningitidis*, discovered in 1887 by Weichselbaum in six cases that he examined, and subsequently found in other cases by Goldschmidt, Guarnieri, Netter, Faber, and others.

Pathological Anatomy.—The gross changes may vary from those that are not recognizable macroscopically to collections of greenish pus in the subarachnoid space one-half inch or more in thickness and covering the entire surface of the brain. In the slightest forms the presence of the condition may be suspected by the slight edema of the arachnoid, and perhaps a small collection of fluid containing flakes along the fissures of the brain. In some cases, however, even this does not occur, and it is impossible, without a microscopical examination, to

say that inflammatory processes exist. Microscopically, sections in these cases usually show overfilling of the small vessels with blood, and a greater or less number of round cells, usually polynuclear, immediately surrounding it. Often this collection of round cells is most marked in the recesses of the convolutions. Staining for bacteria usually reveals the presence of a few, although in these cases they are rarely numerous. If the process has been more severe, or of longer duration, the edema of the arachnoid becomes more pronounced, its glassy, moist appearance being very distinctive. The vessels are usually injected; this applies particularly to the veins, which appear as dark-blue tortuous cords running through the membranes. In the arachnoidal space there is now a considerable collection of fluid, and along the sides of the arteries usually a distinct collection of lymph or pus. Sometimes, but not always, the arterioles are also distinctly injected, and occasionally there is a faint pinkish coloration, due to the injection of the capillaries.

This form may be localized or diffuse, and is almost always secondary to some local source of inflammation, which is most frequently middle-ear disease. The process often shows distinct indications of rapid extension, and may spread to the lining of the ventricles and cause an internal collection of fluid.

The diffuse forms have been divided, according to the part affected with greatest intensity, into leptomeningitis of the vertex and leptomeningitis of the base. The processes are by no means limited to these areas, however, but may extend in any direction. It is common for the suppurative lesions to spread along the arachnoid spaces to the spinal meninges. The ventricles may be attacked by way of the blood-vessels of the choroid plexus.

The changes observed consist of diffuse injection of the soft membranes, edema of the arachnoid, and a perivascular serofibrinous exudate along the course of the vessels coming from the veins. Microscopically, sections show around these vessels a mass of fibrin, in which are embedded a considerable number of polynuclear leukocytes. Often cells undergoing fatty degeneration are also found in these masses, lying close to the walls of the vessels in the portions of the brain where the changes are most pronounced. In this condition micro-organisms are usually found quite readily, either within or without the cells, those within the cells, in particular, frequently showing a partial loss of staining power that has been taken to indicate phagocytic activity.

In the most severe cases the entire subarachnoidal space is distended with a purulent accumulation. The surface of the brain can no longer be seen, the thick greenish exudate covering the convolutions as a smooth mantle. In nearly all these cases there is also pronounced edema, the arachnoid looking thick, shiny, and moist. Microscopical sections show the ordinary picture of a purulent accumulation; pus-cells in a fibrinous meshwork, desquamated endothelial cells, and micro-organisms. In all forms of acute leptomeningitis petechial hemorrhages into the arachnoid are common. The substance of the brain and cord may also be involved (meningo-encephalitis, meningomyelitis), and

this involvement may vary from a slight increase of the neuroglia elements just beneath the pia to the presence of foci of round cells. These foci are usually found about the small vessels or lymphatics dipping in from the pia, the latter situation being by far the more frequent. Ordinarily they are microscopical and surrounded by a narrow zone of partially degenerated nervous substance, outside of which there is again a slight increase in the neuroglia tissue and cells. Occasionally, however, the cerebral involvement may be more extensive, and large abscesses are formed, leading to the destruction of considerable portions of the nervous substance. The nerve-fibers, even those in the neighborhood of the lesion, rarely show distinct alterations. The ganglion-cells, however, exhibit slight diffuseness in taking the stain, or irregularities in the arrangement of the chromophilic bodies. If the abscesses are larger, either involving or close to the gray substance, the ganglion-cells may show extensive degeneration, with entire loss of staining power and fragmentation of the protoplasmic processes, nothing being left to indicate the position of the cells excepting an irregularly shaped vesicle containing some brownish pigment. These larger foci, however, are usually found in the white substance.

An attempt has been made to distinguish varieties of meningitis according to the infective agents, and Netter has stated that in pneumococcic infection the pus is viscid and greenish; in streptococcic infection, more serous and less adherent to the membranes. Influenzal meningitis is said to be commonly accompanied by pial hemorrhages and a perivascular infiltration extending rather deeply into the gray matter. Honl believes that only four forms can be differentiated—the thick, viscid pus of the pyogenic micro-organisms, the yellowish exudate of tuberculosis, the bluish-green pus of the *Bacillus pyocyaneus*, and the purulent exudate containing yellowish grains of actinomyces.

Epidemic cerebrospinal meningitis does not differ essentially from the ordinary septic form, excepting in its cause, the meningitis coccus (*q. v.*). As a general rule, the inflammatory process begins upon the convexity of the frontal lobes, and proceeds backward and downward, the basal meninges being involved late in the course of the disease. Aside from those forms occurring as a complication of other pathological conditions that lead to death before the meningitis has been fully developed, it is the one most likely to kill the patient before distinct alterations have become evident. These cases are spoken of as *foudroyant* or *fulminant*. The disease is often accompanied by lesions in other parts of the body, as petechiæ in the skin, suppuration in the joints, multiple abscesses, endocarditis, degenerations of the myocardium, and suppuration of the labyrinth of the ear.

Associated Changes.—Besides the meninges of the brain, those of the cord are almost always involved, even in cases of tuberculous meningitis. The peculiarities of these conditions are described in the section on the spinal cord. Extension along the fold of pia mater that covers the choroid plexus is also common. The cerebrospinal fluid may be turbid, there is a moderate amount of lymph on the ependyma

and over the surface of the plexus, and the latter may even contain small abscesses. Not infrequently, in prolonged cases, meningitic adhesions and occlusion of the aqueduct of Sylvius give rise to an acute hydrocephalus.

Chronic leptomeningitis, a rare condition, may follow an acute attack or arise as a part of productive pachymeningitis or as a part of the chronic infections. It is commonly hypertrophic in form, leading to meningeal adhesions and involvement of the outer layers of the cerebral cortex in fibrous changes. The basilar form is perhaps the commonest, although a disseminated chronic meningomyelitis is usual in paresis.

INFECTIOUS DISEASES

Tuberculous meningitis is usually a manifestly secondary affection, although in children it may occasionally appear in connection with a few recent foci in other parts of the body. The bacilli ordinarily reach the meninges by the blood-vessels, particularly, in all probability, by the left carotid, from which situation they may spread along the base or to the vertex. Occasionally they seem to pass up the vertebral arteries, and may then affect the cerebellum more severely than the base of the cerebrum. Tuberculosis may also extend directly from tuberculous lesions of the skull or of the middle ear, and it has occasionally been observed to occur after traumatism. Other routes of infection, however, have been suggested, particularly, as in acute purulent meningitis, the organisms have been supposed to pass up the posterior mediastinum, the retropharyngeal areolar tissue, and thence into the cranial cavity. Mixed infection not infrequently occurs, and has been supposed to account for the purulent exudate. It is certain, however, that pure tuberculous meningitis may at times occasion the formation of pus. The organism that is most frequently found in connection with tubercle bacillus is the pneumococcus, and it may be found intimately associated, although it has been stated that the tubercle bacillus appears to predominate at the base of the brain and the pneumococcus in the exudate of the convexity.

Pathological Anatomy.—In cases that die of pulmonary tuberculosis it is not uncommon to find, particularly in the pia upon the convexity, a number of small grayish nodules. These are not always apparent upon superficial inspection, but by cutting through the cerebral hemisphere as far as the pia, and then stripping it away from the under surface of the membrane and holding the latter up to the light, they may readily be seen. In certain cases tubercle bacilli have been found when recognizable macroscopical lesions were entirely absent. Microscopical examination usually reveals a few masses of epithelioid cells and some slight perivascular round-cell infiltration.

When the infection is more severe the tubercles are usually most numerous upon the base of the brain, particularly on either side of the carotid canal and in that part of the base just posterior to the dorsum sellæ. Ordinarily the disease assumes the form of disseminated miliary

tuberculosis. The tubercles are situated between the arachnoid and the pia, often in the depths of the sulci. They vary in size up to 0.5 cm. in diameter, and often show slight cheesy degeneration in the center. The meninges are congested, and usually there is an exudate of inflammatory liquid that contains flocculi of lymph, or is even seropurulent in character. Microscopical examination shows that the tubercles are composed of epithelioid cells, which occasionally seem to be dividing. Giant cells are also present, although perhaps not so frequently as in lesions in other parts of the body. There is usually round-cell infiltration about the vessels, and the latter are apt to be distended. This round-cell infiltration may also extend into the cortex of the brain, and the tubercles are often found in the latter situation. Tubercles may also exist in the choroid plexus. Sometimes, if the process has lasted for some time and the tuberculous masses have increased in size, they may undergo cheesy degeneration and form irregular masses; these are usually found at the base of the brain, and often cause serious pressure upon the cranial nerves that they involve.

Occasionally, when only a small number of bacilli have reached the meninges and have been deposited in one point, a single cheesy nodule may be found, particularly in one of the sulci, forming the meningeal *tyroma*, which sometimes attains a considerable size. In these less acute cases the exudate is considerable, and involves not only the subarachnoidal space, but also the ventricles of the brain, causing a condition that was formerly described as *acute hydrocephalus*. Numerous tubercles are found in the choroid plexus, and the ependyma is covered with slight elevations resembling somewhat the appearance of *cor villosum*. These are usually found to consist of proliferated epithelial cells and of the subependymal neuroglia and fibrous tissue. Tuberculous infiltration of the brain substance is, however, very common. This may be either nothing more than an extension by continuity along the lymph-spaces and blood-vessels dipping from the pia or ependyma into the brain substance, and giving rise to small foci composed of epithelioid and giant cells surrounded by leukocytes, and perhaps exhibiting a slight degree of cheesy degeneration in the center; or else considerable areas of softening, which are perhaps caused by the formation of thrombi. These are most frequent in the corpus striatum and the crura, and appear as grayish-white or yellowish areas of softened and degenerated nervous tissue. Not infrequently, punctiform hemorrhages are found in the cortex about these areas of softening. In general, extension of the tuberculous process to the meninges of the cord occurs if the duration of the process is at all prolonged, but the vertebral canal is so much longer than the spinal cord that pressure symptoms rarely occur, and, as the irritation is slight, the cranial symptoms dominate the clinical course.

Syphilis may occur in the form of gummatous infiltration and diffuse inflammations. In the former instances there are found flattened nodular thickenings of the arachnoid and pia, of grayish or pinkish color, and tending to undergo necrotic change. The process begins in the inner surface of the arachnoid, or sometimes in the walls of the blood-

vessels, and extends to the pia and cerebral substance on the one hand and to the dura on the other. In another form of syphilis there is diffuse infiltration or syphilitic leptomeningitis, causing considerable thickening of the meninges. The characteristic of these conditions is the concomitant obliterating endarteritis. The lesions of syphilis are like those of tuberculosis, but the endarteritis, periarteritis, and the characters of the giant cells help in the diagnosis. The syphilitic giant cells do not have the typical peripheral or polar nuclei. Nevertheless the diagnosis is often exceedingly difficult.

Chronic syphilitic leptomeningitis and meningo-encephalitis are occasionally met with. In these cases the membranes are thickened

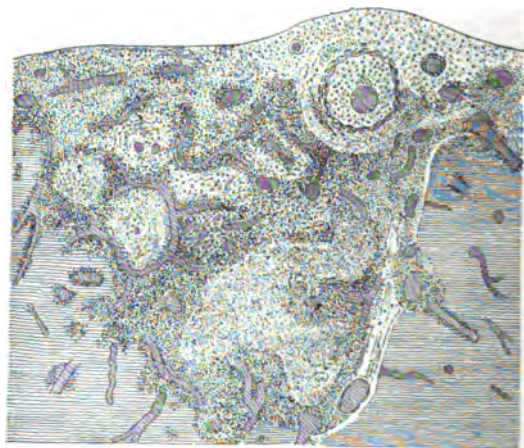


Fig. 421.—Gummatous meningo-encephalitis (Ziegler).

and fibrous, and secondary extension of the infiltration into the cerebral cortex occurs (Fig. 421).

TUMORS

The Pacchionian Bodies.—The most common, and clinically perhaps the least important, tumors of the arachnoid arise in the Pacchionian bodies. These are small granular masses or circumscribed nodules, chiefly along the edge of the superior longitudinal sinus, but often extending a short distance laterally over the convex surface of the convolutions. Microscopically they consist of dense masses of fibrous tissue, covered by a layer of proliferated endothelial cells, which give them a concentric structure. Occasionally some calcareous nodules may be found in them. They may undergo active hyperplasia and grow outwardly, frequently eroding the skull, and giving rise to little pits upon the inner surface.

Endotheliomata are most frequently found in the pia mater. They are supposed to arise from the perivascular tissue or the arachnoid. They present irregular alveoli, lined with cuboidal or round endo-

thelial cells. These are not always arranged in a single layer, but may occasionally fill the alveolus, although this is not common, and more frequently some have broken loose and lie free in the cavity. The cells often show karyokinetic changes, and occasionally alterations in shape, due to mutual pressure. These tumors resemble carcinomata closely, but the presence and proliferation of the epithelium-like cells in the stroma, such as occur in carcinoma, have not been observed (Fig. 422). They are soft gray or red, flat spreading masses.

Sarcoma of the ordinary kinds may occur in the pia. Angiosarcomata with and without degenerative changes are reported. Bone may be laid down in pial tumors (psammoma). Carcinoma does not



Fig. 422.—Perithelioma of meninges.

occur, but tumors resembling it will be discussed under ependyma and ventricles.

Cholesteatomata are terata, and have been observed in two related forms: those consisting exclusively of squamous epithelial cells, and those containing, in addition, various other epidermal structures, such as hairs or sebaceous glands. They are usually situated in or about the median line of the calvarium; at the base of the brain; on the upper surface of the corpus callosum; or somewhere along the choroid plexuses. Those containing hair are most frequently found near the cerebellum, growing either from the arachnoid, or, more rarely, from the outer surface of the dura. Those arising from the dura may occur upon the frontal or occipital bones, and often show calcareous infiltration, or even true osseous formation.

Lipomata are rare. They are usually found in children, and always in the soft membranes, especially the pia mater. The most frequent seats are the upper surface of the corpus callosum and the corpora candicantia. According to Bostroem, they are probably epidermal in origin, nothing but the subcutaneous fatty tissue being left.

Teratomata.—Growths of more distinctly teratoid character than the cholesteatomata, above described, are occasionally found. Chiari has described a case that grew from the lining membrane of the third ventricle in an infant that died at the age of seven weeks. It consisted of a medullary white mass and a number of serous cysts. The solid substance was composed of fetal brain substance, in which were fissures lined with epithelium similar to that of the central canal of the cord, and ganglion-cells, retinal cells, skin-glands, and jelly of Wharton. Fibrous and cartilaginous tissues were also present.

THE BRAIN

DEVELOPMENT AND ANATOMY

Development.—(For convenience, the development of the cord is considered in this place with that of the brain.) The central nervous system commences as a shallow depression, that appears in front of the primitive streak in early embryologic existence. It is bounded on either side by ridges, known as the *medullary folds*. The groove gradually becomes deeper, and finally the two medullary folds unite, giving rise to the formation of the *medullary canal*. The canal is first formed in the portion that subsequently forms the cervical region of the spinal cord. Just beneath the medullary canal there is a cylindrical collection of cells, often with a small cavity in the center that forms anteriorly a shallow groove, the so-called notochord. Its function is unknown, and it eventually disappears during embryonic existence. The anterior extremity of the embryo continues to grow, and bends downward, forming the cephalic fold. In this part of the neural canal three dilatations occur—the *primary vesicles of the brain*; the posterior portion ultimately forms the spinal cord.

The Cord.—At first the wall of the embryonal cord is composed of a single layer of cylindrical epithelial cells (*spongioblasts*), with nuclei at various distances from the central canal; these ultimately become the nuclei of the glia-cells. The central ends remain cylindrical; the peripheral ends become branched, forming the myelospangium, probably the antecedent of the neuroglia fibers, which, according to some investigations, become separated from the cells. At the age of about five weeks in the human embryo, certain cells, with a considerable amount of clear protoplasm, are found near the inner limiting membrane, the so-called *germinal cells*. Subsequently other cells appear, probably derived from the germinal cells, as they are first found in the situations occupied by these, the so-called *neuroblasts*. These are distinguished by the appearance of a projection, pointing toward the periphery of the spinal cord, that grows out from the protoplasm and ultimately pierces the external limiting membrane to become an axis-cylinder.

Just outside of the cord, probably from masses of epiblastic cells derived from its wall, the cells of the spinal ganglia appear. These are, at first, bipolar, one process extending into the spinal cord and the other peripherally, but ultimately the two processes unite at their commencement. The spinal cord at first completely fills the spinal canal, but after the fourth month the vertebral column begins to grow somewhat more rapidly, and at birth the conus terminalis is opposite the third, and in the adult extends only to the lower end of the first, lumbar vertebra. The nerve-fibers are at first non-medullated, but later myelin-sheaths appear, first

in certain parts of the posterior columns, and lastly in the pyramidal tracts, which often, at birth, are not yet entirely medullated. The membranes are derived from the mesoblast.

The Brain.—The three primary vesicles from which the brain is developed continue to grow, and the first is subdivided by a median constriction into two secondary vesicles, the prosencephalon and the thalamencephalon. From the former two lateral offshoots appear, which give rise to the cavities of the lateral ventricle, and from the walls of these are developed the cerebral hemispheres, the olfactory lobes, and the corpus callosum. The cavity of the second vesicle forms the third ventricle, and from its walls grow the nervous structures of the eye, the optic thalami, and the pituitary and pineal bodies. The cavity of this vesicle (mesencephalon) forms the aqueduct of Sylvius, and from its walls grow the corpora quadrigemina and the crura. The posterior primary vesicle also becomes constricted, forming the ependymophalon and the metencephalon. The two cavities, however, remain united and form the fourth ventricle. From the walls of the anterior portion are developed the cerebellum and the pons. From those of the posterior portion, the medulla oblongata.

The ultimate shape of the brain, however, is largely determined by certain flexures and by the growth and extension of the axis-cylinders, which pass in various directions and form the white matter, the greater bulk of the central nervous system. Differing from the cord, the growth of the brain exceeds that of its containing bony capsule. As a result the surface of the hemispheres is usually thrown into folds. The earliest of these appear during the third month, and are usually transverse to the axis of the brain, although not invariably. The lateral ventricles at this stage are very large, and the sulci project into their cavities as ridges. During the fourth month the deep fissures disappear, with the exception of three—the Sylvian, the calcarine, and the parieto-occipital fissures. The hippocampal fissure also appears about this time. The other permanent sulci appear about the end of the fifth month, the earliest being the fissure of Rolando; but many of the secondary fissures do not develop until after birth.

The *sympathetic nervous system* is probably only an offshoot of the central nervous system. The cells first appear upon the spinal nerves, from which they wander, remaining connected with them by short branches, the rami communicantes. Some authorities, however, believe that the sympathetic system is developed from the mesoblast.

Anatomy.—The brain consists of the two cerebral hemispheres, the basal ganglia, the pons, the medulla, and the cerebellum. Its weight varies from 1200 to 1300 grams in the adult female, and from 1300 to 1400 grams in the adult male. Its consistency at birth is very soft; in the adult it becomes somewhat firmer, but is always softer than the normal liver. Its color varies from grayish white in the parts composed of medullated fibers to reddish gray in those composed chiefly of ganglion-cells. The cerebral hemispheres are separated by the superior longitudinal fissure, and united by the corpus callosum and the anterior commissure. They are joined to the pons by the crura. Their surfaces are rendered very irregular by the presence of numerous fissures or sulci, and are divided into the frontal, parietal, occipital, and temporosphenoidal regions. The important fissures are the Sylvian, the Rolandic, and the parieto-occipital on the external surface; the calloso-marginal, the calcarine, and the parieto-occipital on the medium surface.

The hemispheres are composed essentially of an outer layer of gray matter, the cortex, containing ganglion-cells, and of fibers passing from these in various directions and uniting them with other parts of the central nervous system. These may be divided into three main classes: the *projection fibers*, passing between the cortex and the basal ganglia, or into the internal capsule; the *transverse* or *commissural fibers*, passing between the two hemispheres; and the *association fibers*, passing between different areas in the same hemisphere. The most important clinically of the projection fibers are those which arise in the motor portion of the cortex, and pass first into the internal capsule, where they are grouped about the knee, thence through the crura and the pons, to form ultimately the pyramids of the medulla. They decussate in the first cervical segment of the cord and form the pyramidal columns of

the cord. The fibers of the optic radiation commence in the cortex about the calcarine fissure and in the cuneate lobe, and pass forward to the pulvinar of the optic thalami. They are also associated with the external geniculate body and the anterior corpus quadrigeminus. From the pulvinar, the optic tracts pass around the crura, then lie below and to the inner side of the internal capsules, and unite in front of the tuber cinereum to form the chiasm from which the optic nerves arise.

The transverse or commissure fibers include those of the corpus callosum and of the anterior commissure. The fibers in the corpus callosum appear to correspond closely to those regions of the brain situated nearest to them. The anterior commissure is composed of fibers uniting the temporosphenoidal lobes of the two hemispheres.

The association fibers either connect adjacent lobes (*fibrae propriae*), or unite distant portions of the hemispheres (the long association fibers).

In the substance of each hemisphere are found the lateral ventricles: two long, narrow, branching cavities, joined to the third ventricle by the foramen of Monro. Each contains a choroid plexus, and is normally lined with epithelium and contains clear cerebrospinal fluid. The anterior portion of the two ventricles is separated by the septum. A small double layer of epithelial cells line and almost fill the cavity of the third ventricle. The basal ganglia of the brain are the lenticular nucleus, the caudate nucleus, forming together the corpus striatum, and lying on either side outside of the internal capsules, the optic thalamus, a large oval mass lying beneath the caudate nucleus. To the outer side of the lenticulate nucleus is a band of white fibers, known as the external capsule, that is separated from the cortex by a thin layer of pigmented cells, the claustrum.

The third ventricle communicates with the fourth by a narrow canal, the aqueduct of Sylvius, which passes through the tegmentum of the crura. It is surrounded by a zone of gray matter, in which are found the nuclei of the oculomotor nerves. Above it are the four corpora quadrigemina, two pairs of rounded eminences with a white cortex and a gray center. The superior corpora, as has been already stated, are intimately connected with the optic tract. Just anterior to these bodies is the small pineal gland, situated above the posterior commissure. Externally to the crura on either side, continuous with the posterior portion of the thalamus, are the two geniculate bodies, separated by the optic tract. The optic thalami lie on either side of the third ventricle and just beneath the caudate nuclei; they are oval bodies containing numerous groups of nerve-cells, the anterior portion being called the anterior tubercle, and the posterior portion the pulvinar.

The two great channels by which fibers pass to and from the cerebrum are the crura cerebri. These are divided by a narrow layer of dark-gray material, the substantia nigra, composed of pigmented ganglion-cells, into the crura or inferior portion, and the tegmentum or superior portion. A part of the crus is formed, as has already been stated, by the pyramidal tract. Sensory nerve-fibers are found in two groups in the tegmentum toward the outer edge, comprising the inferior and superior fillets.

The two crura unite to form the pons, which is composed, ventrally, of bundles of motor fibers separated by the commissural fibers of the cerebellum, and dorsally, partly of the fibers of the fillet and partly of gray matter. Below the pons is found the medulla, which is really nothing but the upper portion of the spinal cord. Anteriorly we find two well-defined bundles of motor fibers, the pyramids; just back of these the lower olives; and on the dorsal surface the nuclei of the tenth and twelfth nerves, and externally to them the nucleus gracilis and nucleus cuneatus, the terminations respectively of the columns of Goll and Burdach of the cord. The axis-cylinders of the cells that compose these nuclei pass toward the brain and form the fillets. On the outer surface of the medulla, near the dorsal surface, are the two restiform bodies, the continuations of the cerebellar peduncles.

The cerebellum is composed of two lobes and the vermiform process. Upon cross-section it is seen to be composed of a great number of narrow gyri separated by deep ramifying sulci, each convolution being lined externally by medullated fibers, beneath which is a layer of ganglion-cells enclosing a center of medullated

fibers. It is united to the cerebrum by the superior peduncles, which terminate in the nucleus ruber of the tegmentum. The middle peduncles form the transverse fibers in the pons, and the inferior peduncles pass into the restiform bodies of the medulla. Certain nuclei are found in the interior of the white substance, of which the most important is the dentate nucleus, analogous structurally to the olives of the medulla.

The Neuron.—Histologically, the essential element of the nervous system is the neuron. This, in the sense of Waldeyer, comprises the nerve-cell, its protoplasmic processes (which are branched), and the axis-cylinder, or axone, which may be a single fiber giving off angular collaterals, or is extensively branched (Golgi cells). The cell-body consists of protoplasm without a distinct cell wall, and containing or not containing chromophilic bodies. According to Nissl, two groups of cells are thus formed, the somatochromes with, and the caryochromes without, these bodies. According to zoölogists, these are respectively motor and sensory in function, but the cells of the spinal ganglia, which appear to be sensory, contain these granulations. Cells are spoken of as multipolar or bipolar, according to the number of processes that project from them. It is impossible to describe in this place all the varieties of cells and their distribution in the nerve substance. The neurons may be divided into endogenic, wholly within the central nervous system, and exogenic, partly in the peripheral nervous system. Each axis-cylinder terminates in a tuft of fibers that surround, without touching, some other ganglion-cell, or, if it extends to the periphery, terminates in a special sensory corpuscle or a muscle-plate. Upon emerging from a cell the axis-cylinder becomes surrounded by a sheath of myelin, while about several axones and their covering a fibrous coating, the sheath of Schwann, appears.

Nerve-cells and fibers are supported by a special tissue, glia-cells and their inter-lacing fibrils. The cells are small, deeply staining, and of round or irregular shapes, beset with numerous delicate branches. In the white matter these cells are called "spider cells," and have stiff straight processes, while in the gray matter the branches are more irregular and are subdivided. There is beside these cells a small amount of ordinary connective tissue.

Physiology of the Brain.—This subject can be touched upon only very briefly. The brain is the organ in which all the intellectual processes are performed, but it is as yet unknown how this is accomplished. A number of theories have been suggested, but none of them are based upon observed fact. We are better informed concerning the origin of certain specific motor impulses in the brain, and the regions where stimuli from certain of the special sense organs are received. The motor region is situated in the two gyri on either side of the fissure of Rolando, and in the posterior portions of the three frontal gyri. In general, it can be said that the centers are arranged so that the cells sending fibers to the highest portion of the body—that is, the face, eyes, etc.—are situated in the lowest portion of the motor region; and the cells sending impulses to the lowest portion of the body—the feet, for instance—are situated in the highest portion of the motor region along the superior longitudinal fissure. This region has been mapped out by the aid of direct observation, not only upon the lower animals but upon human beings. Any irritation causes movement of the corresponding portion of the body, the movement being of a co-ordinated and not of an individual muscular type; that is to say, the stimulation of a center in this region causes contraction of a number of muscles, with the object of accomplishing some definite movement. The fibers of the motor region constitute the pyramidal tract, whose course has already been described. Irritative lesions of the motor cortex produce convulsive explosions, clonic in type, usually described as epileptic. If the lesions are sharply circumscribed, and the convulsions occur always in a certain definite group of muscles, the condition is spoken of as Jacksonian epilepsy. Destructive lesions cause paralysis of a spastic type; that is to say, the lower motor neurons evidently suffice to maintain a condition of contractility in the muscles, which may be exalted either as a result of some irritation exerted by the degenerated central motor neurons, or because, under normal conditions, the central motor neurons exert an inhibitory or restraining action. We are still in ignorance concerning the localization of the sensory impulses. The effect of lesions in the upper portion of

the parietal lobe in producing sensory forms of muscular inco-ordination has led to the supposition that the fibers conveying muscular sense terminate in this region. It is practically certain that the great majority of the sensory fibers terminate in the optic thalamus, from which other fibers proceed to the cortex; but as brain physiologists are practically agreed that all the active intellectual processes are accomplished in the cortex, it is supposed that the thalamus is merely a situation in which some alteration or modification of the impulses received from the periphery occurs. Regarding the special senses, the visual impressions terminate in the cuneus. The auditory centers are situated in the superior temporosphenoidal convolutions, and the destruction of these centers produces loss of understanding of sounds heard—that is to say, sensory aphasia. The centers for olfaction are situated in the uncinate gyri. Irritation of these regions has in some cases apparently given rise to subjective odors, usually disagreeable. They may occur as the *auræ* of epileptic attacks. The center for taste has not been located, although it is probably in this region. The functions of the remaining portions of the cortex are practically unknown. It is supposed that the intellectual processes are performed chiefly in the frontal lobes. At any rate, extensive lesions of these lobes have caused alterations in character—loss of the faculty of attention, more or less stupidity, and hebetude. Occasionally ataxia is present. The relation of pathological processes in the brain to insanity is not well determined. Lesions have, of course, been found in parietic dementia, in acute delirium, and in idiocy, but examination of the brain in cases of paranoia and melancholia has been practically negative. The functions of the other portions of the brain are not well determined. The basal ganglia are apparently merely stations in the paths of the fibers, chiefly those of sensory nature. The anterior corpora quadrigemina have something to do with the fibers of the optic tract, and in them is probably situated the center of the pupillary reflex to light. The external geniculate ganglia are apparently associated with the fibers conveying auditory impressions. The pons contains the ganglion-cells of the peripheral motor neurons of the eye-muscles, but is otherwise merely a pathway for various tracts of fibers. The medulla contains the ganglion-cells of the cranial nerves, and, in addition, all the tracts of fibers passing between the brain and cord. The functions of the cerebellum are not well known. There is no doubt that it has something to do with equilibration, but the lesions must be situated either in the vermis or bilaterally.

POSTMORTEM DEGENERATIVE CONDITIONS

It is important to be acquainted with the postmortem alterations that may take place in the nervous system, in order to avoid the confusion of such changes with those that have occurred as the result of disease. Little attention has been paid to the macroscopical changes, and they are not characteristic. Their degree depends upon the temperature at which the body has been kept after death, the nature of the disease that preceded death, and the period that elapsed before the tissues are removed. Ordinarily no changes will be noticed under thirty-six hours if the body is kept on ice. If kept at a temperature of about 16° C. (61° F.), the brain and cord will appear normal if removed within twenty-four hours. There is first softening of the nervous tissue that is general and not associated with pigmentation; the tissues may become so soft that it is almost impossible to remove them without injury. Later, there is often a considerable extravasation of blood-pigment around the vessels; and, finally, if putrefaction is advanced, the tissues become almost diffuent and light brown in color.

Italian authors have studied methodically the microscopical changes. The nerve-cells swell, their protoplasmic processes break off, and there is a gradual loss of the staining power of the chromatin bodies; vacuoles appear in the protoplasm and the outline of the cell becomes irregular, and finally the chromatin substance completely disappears. The outlines of the nucleus become indistinct, it swells, and then contracts, with irregularity of the outline. It stains homogeneously, due to diffusion of the chromatin, and may contain small granules of hyaline material. Later it loses its staining power, and finally disappears completely. The nucleolus is the

last structure to show alteration; it may swell slightly, become filled with vacuoles, and then break up into granular material and disappear. The protoplasmic processes do not exhibit varicosities, but apparently become more fragile, and are very apt to be broken off during staining. Changes may take place in the myelin-sheaths that, when studied by Marchi's method, are not greatly different from those seen in areas of softening—that is, small fatty granules appear along the course of the nerve-fiber. In postmortem lesions there is no perivascular round-cell infiltration; no compound granular cells can be found in the tissue; there are no signs of proliferation in the neuroglia, and the process is more general and uniform than is apt to be the case in morbid conditions.

CONGENITAL ABNORMALITIES

The deformities of the brain are numerous and complicated. They may be divided roughly into those associated with alterations in the skull and those occurring within the cranial cavity.

Acrania is a deformity characterized by absence of the skull. The membranes are usually preserved and form a sac filled with serum, on

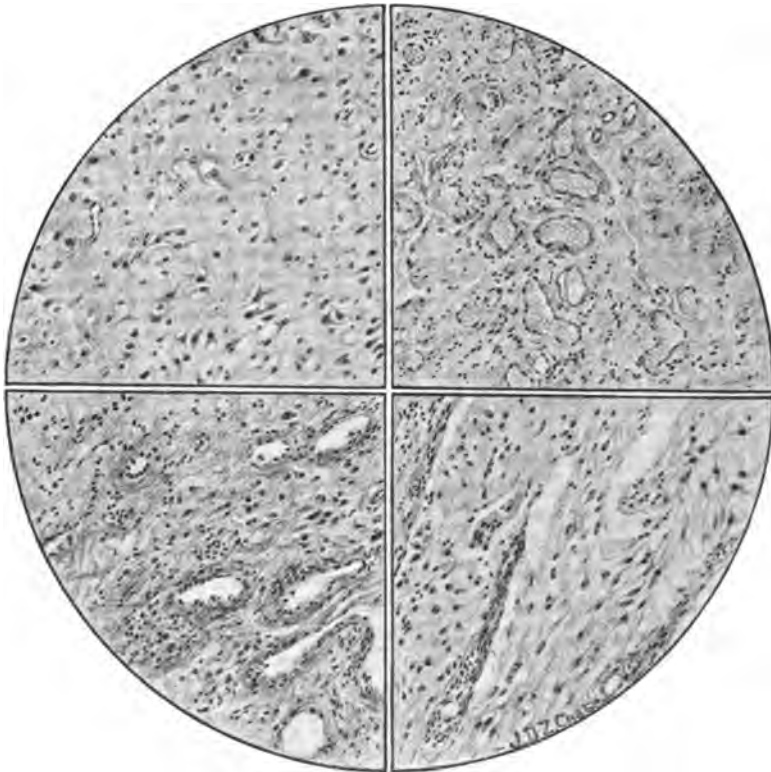


Fig. 423.—Meningo-encephaloma which grew in a meningocele into the nose. Note the cerebral, meningeal, and glial elements.

the inner surface of which small particles of nervous tissue may occasionally be found. More frequently the brain forms only a small mass at the upper portion of the spinal canal, lying on the basilar process

of the occipital bone. Sometimes it appears as if the sac had ruptured or had never completely closed, for the membranes are collapsed and form upon the base of the skull a mass consisting of fibrous connective tissue and blood-vessels. Often in this case the encephalon is entirely absent, but the pons and medulla may be almost completely developed. The cranial nerves are present.

Hemicrania is a condition in which more or less of one of the parietal bones, or of a portion of the frontal or temporal bone, has failed to develop. The corresponding portions upon the opposite side that have developed are usually hypoplastic. Ordinarily, anencephaly, or else partial development of the brain, is associated with these changes.

Cranioschisis is the name applied to imperfect closure of the skull along the middle line. This may be associated with *rhachischisis*, in which case both skull and spine are cleft. The commonest situations for small fissures are in the frontal bone, in the region of the posterior fontanel, in the median line of the posterior portion of the occipital bone, and, more rarely, in the region of the anterior fontanel or the sagittal suture, or in the sphenoid bone.

Fissures or other small defects usually occasion hernia of the brain, which is named *encephalocele*, and according to its situation anterior or posterior, frontal or occipital, superior, inferior, or lateral. If, instead of brain substance, only the membranes protrude through the fissure, the condition is known as *meningocele*. In these cases the cavity is filled with cerebrospinal fluid. Sometimes the under surface of the membrane is lined with nervous tissue, showing that it represents a dilatation of one of the primary cavities of the brain, corresponding to the condition found in *spina bifida*. These congenital herniæ are probably the result of *fetal hydrocephalus*, although it is possible that the chief cause is the imperfect development of the cranium. In cases in which the fissure is in the sphenoid bone, it is not uncommon to find, as an associated condition, cleft palate. Life is, of course, incompatible with extensive *encephalocele*. If it is small, the neck of the sac is sometimes constricted, either spontaneously or as a result of surgical interference, and recovery ensues.

Cyclencephaly is a peculiar deformity in which there is failure of the anterior cerebral vesicle to develop. The frontal lobes remain fused and one rudimentary central eye develops (*cyclopia*).

Abnormalities in Size.—The size of the brain is subject to considerable variation.

Macrocephaly is the condition in which the brain is excessively large—that is, more than 1500 gm. This may be of two kinds. In the first, and perhaps less common, form the brain is entirely normal in structure, the proportion between the various parts being maintained and the relation between the nervous tissue and the neuroglia not altered. In some instances the subjects possess unusual intelligence; in others this is not the case. The second form is enlargement of the brain with hyperplasia of the neuroglial tissue. This is not infrequently found in the so-called *hypertrophic nodular gliosis*. In this condition the brain

may be considerably enlarged, and the convolutions may be increased in size, although not abnormal in arrangement. Microscopically, the changes described in the section on sclerosis are discovered. A pseudo-enlargement of the brain is produced by hydrocephalus. The weight of the brain, after the liquid has been removed from the cavities, is usually less than normal, although this is not always the case.

Hypertrophy of the brain may be limited to certain parts. These are usually individual gyri, and are nearly always sclerotic. Sometimes only a portion of a convolution is thus affected, and produces a tumor-like swelling. Hypertrophy of individual sections of the encephalon, such as simple enlargement of the cerebellum, or of one of the cerebral hemispheres, does not appear to have been observed.

Microcephaly is a condition in which the brain is much smaller than normal, as a result of defective growth or early fusion of the skull bones limiting the development of the encephalon, or else of disease, either in early life or later. In some instances the brains, aside from their smallness, appear perfectly normal, and this diminution in size, within certain limits, is not incompatible with normal intelligence. Usually, however, there are sclerosis and decrease in size of some of the gyri. There are, of course, the associated changes usually found in sclerotic conditions.

Hypoplasia of individual portions of the brain has been observed, particularly of the corpus callosum, the cerebral hemispheres, and the cerebellum.

Hypoplasia of the *cerebral hemispheres* is usually due to some pathological change, and will be discussed under sclerosis and porencephaly.

The congenital absence, either total or partial, of the *corpus callosum* has been observed in a number of cases. It may occur in brains otherwise normal, but is usually associated with microcephaly or other profound structural changes. In the cases in which no other lesions exist the intelligence may be normal, but in the great majority of instances the patients are idiots. The appearance of the brain is quite characteristic. As soon as it is removed the hemispheres fall widely apart, showing the third ventricle covered with a delicate layer of pia mater. The inner surfaces of both hemispheres are divided by numerous fissures, and appear atypical. In cases of marked hydrocephalus the corpus callosum is extremely thin, and may be torn during the removal of the brain, and this may possibly be mistaken for congenital absence. A careful examination, however, will usually reveal the true state of affairs.

Hypoplasia of the *cerebellum*, or even total absence of one or both hemispheres, has been occasionally observed. It is nearly always associated with sclerosis. A collection of cerebrospinal fluid in part supplies the place of the absent organ. The cerebellum may be of normal shape, and even microscopically show no changes other than diminution in size. More commonly, however, the changes are asymmetrical, one lobe being markedly smaller than the other, and perhaps reduced even to a small papilla. There are often sclerotic changes, with marked atrophy of the cortex and disappearance of many of the

medullated fibers. The corpora quadrigemina may also be altered, but this is not invariably the case.

Other changes of unknown significance that have been described are abnormal arrangement of the convolutions. Of these the most important is the presence of *annectant gyri* across the Rolandic fissure, or the absence of annectant gyri in the parieto-occipital fissure. It does not appear, however, although the claim has been frequently made, that these changes are in any way associated with intellectual peculiarities. Bundles of nerve-fibers, taking an abnormal course, have occasionally been found in the pons and medulla. These seem to be produced by premature decussation of portions of the pyramidal tract, and are of no clinical significance.

Anencephaly, or total absence of brain, is a congenital lesion usually associated with acrania. Sometimes it is associated with total absence of the spinal cord; in other cases a portion of the pons, medulla, and the cord are still present, although much smaller than normal. The cranial nerves are usually present, and the eyes, in particular, are nearly always perfectly developed. The lesion is, of course, incompatible with life, although when the medulla is present a few respirations may take place after birth. The appearance of the monsters is very characteristic. From the orbital ridge of the frontal bone the skull slopes in almost a direct line to the neck, making the face and eyes unusually prominent—the so-called frog-face. Frequently other deformities are also present.

Porencephaly is a condition characterized by the absence of a greater or less amount of the substance of one or both of the cerebral hemispheres, leading to the formation of a cavity or cavities filled with cerebrospinal fluid.

Etiology.—The cause of porencephaly is not definitely known. As Von Kahlden remarks, the similarity of the lesions in typical cases is such that it seems reasonable to accept a uniform etiology. Kundrat believed that the lesions were due to anemic infarction, as a result of occlusion of the Sylvian arteries. Von Kahlden, however, believes that it is the result of some disturbance in a development of the brain, and bases his opinion upon the symmetry of the lesions and their peculiar situation. Other authors have suggested an inflammatory origin of the process, because of the adhesions between the membranes. Some cases seem to be due to a failure of blood-supply to the affected part, either by malformation of the vascular channels or endarteritis. A certain number of cases certainly develop after birth; these may be due to injury, such as might be produced by instrumental delivery, or by blows upon the skull, or by embolic or inflammatory processes.

Pathological Anatomy.—Von Kahlden has divided a large series of reported cases into two classes: the typical and the atypical. The former class comprises about two-thirds of all the cases, and is characterized by the presence of a funnel-like cavity in the motor region of the brain, usually bilateral, although unequal, that extends from the subarachnoid space to the cavity of the ventricle (Fig. 424). Frequently this condi-

tion is associated with imperfect development or exposure of the island of Reil. In the atypical form the lesions are exceedingly various; they may be found in any part of the cerebral hemispheres; the shape of the cavity may be either a shallow depression or a deeper loss of substance. Often—in fact, usually—there is no communication between the cavity and the ventricle. These varieties may even be found in the cerebellum, and perhaps are most frequent in the lateral lobes at the point where they unite with the vermiform process. Cases have also been recorded with cavity formation in the base of the brain, communicating sometimes with one of the horns of the lateral ventricles. A sort of cystic formation has been described, in which multiple cavities, not communicating with either the ventricle or subarachnoid space, have been found in the substance of the brain. The macroscopical changes observed in the typical form are as follows: Ordinarily a distinct depression is noticed in the dura after the skull has been removed; when this region is more carefully examined it is found that the dura may or may not be adherent to the arachnoid which covers the cavity. The pia usually dips into and covers the excavation, and may be continuous with the ependyma of the ventricle. The adjacent convolutions of the brain are arranged in a somewhat radiate manner and turn down into the cavity, although this is not invariably the case, for they sometimes may appear as if simply cut off, being otherwise normally arranged. Associated changes in the brain are microgyria; proliferation of the neuroglia tissue, and perhaps also of the connective tissue; atrophy of the nerve-cells in the cortex, particularly of the large pyramidal cells; and more or less complete destruction of the nerve-fibers in the region adjacent to the defect. The spinal cord usually exhibits a secondary degeneration in the pyramidal columns; this, however, is not always the case, for sometimes it appears that one or both pyramidal columns have failed entirely to develop, giving rise to a condition of micromyelia. Other parts of the brain appear to be rarely affected in the typical form of the condition. When the lesion is situated in any other part than the central region, corresponding secondary degenerations may, of course, occur.



Fig. 424.—Porencephaly (case of Dr. J. H. Lloyd).

GENERAL PATHOLOGIC ANATOMY OF THE NERVOUS SYSTEM

The pathology of the nervous system differs from that of the other organs of the body chiefly in the fact that the special structure of which the nervous tissue is composed have no close analogies to the epithelial and connective tissues. It is desirable, therefore, to discuss first the general changes occurring in the nerve-cells, nerve-fibers, and the neuroglia.

The Nerve-cell

On account of their characteristic appearance and sharply differentiated structure, the cells of the anterior cornua of the spinal cord have been most carefully studied, and it is necessary, therefore, that we should give a brief description of their anatomy. The appearance depends largely upon the method of staining employed. By the Golgi method the cell appears as an irregular body, from which come a number of thick processes that rapidly divide and subdivide until they appear as a maze of independent delicate branches, dendrites, upon either side of which can be seen minute projections, the so-called gemmules; from one portion of this cell a fine process arises that is of uniform width, the neuraxon. At regular intervals this gives off the so-called collaterals, delicate branches that spring from it at right angles and have a different course. By this method other ganglion-cells in the nervous system have also been carefully studied and show numerous variations in type, the most important being in the number and complexity of the protoplasmic processes, and the division or even excessive branching of the neuraxon. The morbid changes that can be observed by the application of this stain are but few, since it appears that the pathological cells soon lose their power of impregnation.

Apathy and Bethe, by the employment of certain exceedingly complex staining methods, claimed to have discovered that the nerve-cells are really nothing but stations in the paths of certain delicate fibrilla, called the neuro-fibrils, that pass from one cell to another, not being limited even to the ganglion-cells, but also passing through the neuroglia cells. They therefore believed, and Nissl has agreed with them, that these fibrils are the real functioning elements in the central nervous system, and that the ganglion-cells have probably only some nutritive influence.

The alterations of the dendrites are essentially of two kinds: first, the appearance of *varicosities* upon the protoplasmic processes in their thicker branches; second, the *disappearance of the gemmules* from the terminal filaments. Such alterations have been seen in chorea, in general paresis, in alcoholism, and other forms of poisoning. Sailer found very marked changes of this character in the spinal cords of guinea-pigs killed with tetanus toxin, and Steele described a varicosity upon the axis-cylinder in the cortical cell in an animal killed by diphtheria toxin. Lenhossek appears to regard the varicosities of the protoplasmic processes as the result of an accumulation of the chromophilic bodies, and Kölliker states that they are merely artefacts, a view held by most zoölogists.

In 1885 Nissl described a method for staining the nerve-cells which, on account of its differentiation of the structures of the protoplasm, and the possibility that by it cells in any stage of degeneration may be stained, has yielded most valuable results. It consists essentially of staining tissue, hardened in alcohol, by one of the basic anilin-stains, such as thionin or methylene-blue. The cells of the anterior cornua

show the irregular outline and the numerous protoplasmic processes as before. Throughout the protoplasm are small, irregular bodies, sometimes vacuolated, that take the basic stain intensely. They are arranged somewhat concentrically around the nucleus, but at the points where the protoplasmic processes come off become spindle shaped and turn into them, and are also found in the processes as spindles. Between these bodies the cytoplasm refuses to take the stain, and is called the *achromatic substance*. Nissl and some others believe that it has a delicate fibrillar structure, but this has not been positively determined. A cup-shaped portion of the protoplasm remains clear, and is usually rather sharply delimited from the remainder of the cell. From this extends a long, faintly staining, undifferentiated neuraxon. The nucleus does not stain, but remains as a clear space near the center of the cell, containing a round deeply staining and usually vacuolated nucleolus, surrounded by a membrane with irregular thickenings (Fig. 425). It has been claimed (Kronthal) that these so-called chromophilic

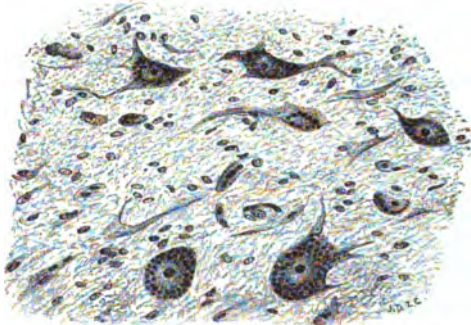


Fig. 425.—Normal and degenerated nerve-cells of the anterior cornua of the spinal cord; $\times 600$.

bodies do not exist in the living cell, but are the products of disintegration. The course of pathological changes appears to be somewhat as follows: The granules become first very irregular in distribution and somewhat finer, so that the concentric arrangement is no longer distinct. They may then diminish considerably in number, so that the cell as a whole appears very much paler; finally, the protoplasm may become entirely clear, a small amount of basophilic substance only remaining that is collected in irregular masses around the nucleus. This also may disappear, and the cell remain as an irregular, faintly and diffusely stained mass in the midst of the tissue. This series of changes is by no means the only one that has been described. Occasionally the chromophilic granules seem to dissolve, although their capacity for staining is unimpaired, resulting in deeply and diffusely staining cells without any apparent structure, excepting the vesicle in the situation of the nucleus (*pyknomorphous state*). Nissl regards these as artefacts, and it is true that they are frequently found in tissues supposed to be healthy. It must not be forgotten that they are always

far more numerous in diseased tissues or in the neighborhood of focal lesions. We have observed some singularly beautiful examples of this change in the brain of a guinea-pig killed by anthrax, in which the micro-organisms were found in the nervous tissue. The solution, with or without loss of staining power, corresponds very closely to the changes observed in the chromatin in karyolysis, and may be very properly described as a sort of chromolysis. In other cases chromophilic bodies may collect in diffuse, irregular masses in one or more parts of the protoplasm, a change which has been observed in the spinal cells of cases of tetanus.

Still another form is the coalescence of the chromophilic bodies, so that each individual one appears larger; their number is less, and they still maintain a rather regular arrangement in the protoplasm. These masses may then further coalesce, giving rise to the appearance just

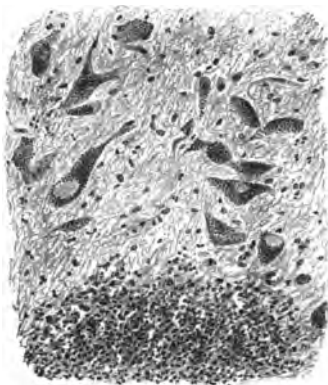


Fig. 426.—Degenerated nerve-cells in the neighborhood of a collection of pus; the granular appearance is due to an excess of pigment; $\times 600$ (case of Lloyd and Sailer).

previously described, or may break up, causing a uniform granulation of the cell, or they may disappear. Berger has attempted to explain most of these phenomena by supposing that the chromophilic bodies are really composed of small granules that are adherent to the sides of the spaces formed by the reticulum of the protoplasm of the cell. If these spaces dilate, the granules will be more widely separated and the appearance will be that of diffuse granulation. If they contract, as occurs in cases of general cellular contraction or so-called inspissation of the cell, they will appear darker and the neighboring ones may seem to coalesce. The changes in the reticulum may be local, and give rise to local alteration in the arrangement (Fig. 426).

Another change that frequently occurs in pathological cells is *vacuolization*. It is possible that a few vacuoles of small size may be the result of the hardening processes. In some cases, however, this alteration is very extensive, the vacuoles reaching $70\ \mu$ in diameter. They appear to be filled with a liquid, possibly lymph, that may undergo slight coagulation-necrosis; at least fibrillæ, that may be fibrin, have been observed. The cells often acquire extraordinary appearances. Indeed, it may look as if the pericellular space was enormously dilated, and that bands of protoplasm extended from it to the surrounding neuroglia. The arrangement of the vacuoles is always exceedingly irregular, and if more than one be present, as is usually the case, the vacuoles vary greatly in size.

Sometimes, instead of the vacuoles, there may be found in the cells masses of some substance that differs from the protoplasm. These are usually homogeneous irregular masses that take the acid stain, and

have been described as "colloid" in nature, using the word in the sense given it to by von Recklinghausen. The true nature of this change, however, is not very clearly understood. Sometimes the vacuoles appear to be replaced by clefts distributed irregularly in the protoplasm.

In nearly all degenerated cells there is accumulation of a peculiar cellular pigment. This may be fatty in nature, as it stains black with osmic acid. In some cases it seems to increase *pari passu* with the disappearance of the chromophilic bodies, so that ultimately the cell appears as an irregular mass filled with this yellowish-brown pigment. It occurs normally in old age, is found in the cells of the substantia nigra of the crura, is an almost invariable accompaniment of those diseases in which a sort of early senility appears to occur, such as general paralysis, and is rarely found in cells undergoing very acute degeneration. Another form of pigment giving the iron reactions occurs in certain pathological states. McCarthy has reported its occurrence in the brain of a rabbit killed by snake-venom.

The changes of the nuclei first appear in the nucleolus; this, as has been said, normally contains one or two vacuoles. In degenerative processes it begins to swell, and more vacuoles develop, so that finally it presents the appearance that has been likened to the morula stage of the ovum. Ultimately, as the degeneration progresses, it may grow fainter and disappear entirely. Clumps of chromatin are often observed at the periphery of the nucleolus, and occasionally ray-like fibers project from them into the nucleus; accessory nuclei are also often present. Two or more nucleoli have also been observed, but it is doubtful if this is a morbid change, although Berkeley contends that it is an invariable sign of irritation.

The nucleus itself exhibits a variety of changes. Stained with hematoxylin, it shows a delicate chromatin reticulum, and this may exhibit, in the ordinary forms of degeneration, changes that are found in other cells in the process of karyolysis; occasionally the chromatin collects in a diffuse, irregular mass about the nucleolus. In various forms of degeneration the nucleus seems to be stimulated, and shows karyokinetic figures, or may even divide completely, so that two nuclei are found in the same cell. This, however, is not necessarily a degenerative change, because similar appearances are found in embryonal and in lacerated nerve tissue. Perhaps the most important nuclear change, and one that is most certainly pathological in nature, is the dislocation of the nucleus. It may be found at the periphery of the cell, or even protruding from it, as if to be expelled. It has been said that the nucleus can disappear from the cell when it does not present marked degenerative changes; it must be remembered, however, that the large diameter of the multipolar cell renders it possible with a good microtome to make a number of sections through a single cell, and it is very likely that these conditions are due simply to sections beyond the plane of the nucleus. In the most advanced types of degeneration the nucleus certainly disappears completely.

Changes may also take place in the cell as a whole. In the process of degeneration its outline usually becomes irregular and angular. The cell appears to be smaller, and often the pericellular space is very obvious. In many cases, however, this is an artefact, produced by the hardening fluid, and although it may be also the result of some morbid process it is impossible to give it any value as such. In the early stages of degeneration the protoplasmic processes may be unimpaired. Varicosities, such as shown by the impregnation, are rarely observed by the Nissl method. One of us has, however, seen them in the nerve-cells of the cord of a guinea-pig killed by tetanus. Tortuosity of the protoplasmic processes is very common, particularly in chronic conditions, such as sclerosis. It is impossible to stain the terminal ends by the Nissl method, and the changes in the gemmules cannot therefore be recognized. Sometimes the processes become friable, break off, and disappear completely, leaving the cells with a rounded outline. Finally, dislocation in the arrangement of the pyramidal cells of the cortex has been observed, particularly in cases of sclerosis of the brain, and it is probable that it occurs in all parts of the nervous system, although when the normal arrangement is irregular it is impossible to estimate its extent.

The functions of the different portions of the nerve-cell are but imperfectly known. The neuraxon conveys impulses from the cells to the periphery, or transfers them in some as yet inexplicable manner in a variety of directions along the collaterals. The cell-body has a distinct trophic influence over the neuraxon, and when this is removed, either by destruction of the cell or by the division of the neuraxon, the peripheral portion of the latter rapidly degenerates. On the other hand, the experiments of Goldscheider, Flatau, and Nissl have shown that the neuraxon exerts at least a temporary influence over the nerve-cell, and when it is destroyed in any way pathological changes invariably occur. There are many theories concerning the function of the nucleus, but no more is really known about it in the nerve-cell than in any other cell. It is concerned in active division, but this is apparently an exceedingly rare occurrence in nerve-cells. The protoplasmic processes have been regarded as nutritive or as centripetal organs. Lenhossek has suggested that the long axis-cylinders that convey impulses to the cells of the spinal ganglia are only a modified protoplasmic process. If this is so, it would be sufficient proof that they have an active function. The fact that the axis-cylinders of other cells terminate in arborization about the dendritic processes, the cells forming the next link in the chain, is also a proof that even the short dendrites receive impulses. The fact that a single particularly thick dendrite may almost always be observed passing to the nearest blood-vessel indicates that they possess also some nutritive function, and that their extensive arborization is partly for the purpose of exposing as great a surface as possible to the nutritive fluid in which the cell is bathed. Concerning the pathological physiology of the nerve-cells we have at present little information, although certain definite changes have been described in cells that have been exhausted

by excessive stimulation. What changes occur in the cell preceding the production of energy have not yet been determined.

The **nerve-fibers** are of two kinds, the medullated and the non-medullated. Non-medullated nerve-fibers consist of the axis-cylinder alone. They are found in the olfactory nerve and in the sympathetic nervous system, and when they undergo degeneration exhibit swelling and varicosities, and ultimately break down into a granular detritus. Non-medullated nerve-fibers may also be provided with a sheath, the neurilemma; such fibers are found in some of the cerebrospinal nerves. Medullated nerve-fibers may consist only of the myelin substance and the axis-cylinder—that is, the neurilemma is absent; such fibers are found in the central nervous system. Ordinarily, they consist of the neurilemma, the myelin substance, and the axis-cylinder; such fibers are found in the central nervous system and in the peripheral nerves. These fibers may branch, either giving off collaterals in their course or forming more or less complex arborizations at their terminations. The axis-cylinder usually exhibits a somewhat fibrillar structure. The myelin material resembles fat and has a high refractive index. It does not extend the whole length of the fibers, but at rather regular intervals is absent (nodes of Ranvier). These points are perhaps for the purpose of providing access for nutriment to the nerve-fiber. Upon the inner surface of the neurilemma are found a few oval nuclei surrounded by protoplasm.

The **function** of the nerve-fibers is comparatively simple. Impulses are conveyed by the axis-cylinder, the neurilemma and the myelin substances apparently serving for protection and perhaps nutriment. It was formerly supposed that the myelin acted as an insulating material; but the fact that non-medullated fibers exist shows that in some cases at least it is unnecessary for this purpose.

The earliest symptom of degeneration in the nerve-fibers is the appearance of granules in the myelin-sheath. These soon run together and form droplets that give all the reactions typical of fat. Such a fiber, examined microscopically in longitudinal section, exhibits these droplets arranged irregularly along its course, giving rise to a somewhat beaded appearance. The next change is usually found in the axis-cylinder. This may swell and become extraordinarily varicose, so that indeed it loses all resemblance to a nerve-fiber. Instead of being fibrillar, it has an irregular granular appearance, and may contain here and there minute droplets of fat, or the fiber may shrink and become granular, and ultimately disappear, nothing remaining to indicate its previous existence excepting a mass of delicate granular detritus. These changes may be brought about either by the destruction of the ganglion-cell from which the axis-cylinder forming the fiber arises, or by separation of the fiber from its ganglion-cell, or by injurious agencies acting locally upon the nerve-fiber. The second form of degeneration—that is, taking place in the peripheral portion of the cut nerve—is known as *Wallerian*. Changes in the proximal end also occur, but rarely extend further than the first node of Ranvier. When a nerve has been

divided the earliest change is found on either side of the point of division, and consists in fragmentation of the myelin. About the third day fat-droplets appear in the myelin; there is some swelling of the axis-cylinder, and often proliferation of the nuclei in the neurilemma may be observed. As the myelin breaks down into a fatty detritus, it is gradually absorbed by the compound granular cells, which appear all along the course of the nerve-fiber, and at the end of three or four months it has entirely disappeared. During this period the neuroglia is undergoing proliferation; at first there is a slight increase in the number of neuroglia cells; later, the proliferation of the fibers preponderates, and, finally, the degenerated area is occupied by a thick mass of coarse fibers that usually undergo slight contraction. The proliferation of the cells ceases about the time that the fibers have become completely degenerated. The subsequent proliferation, if any, occurs only in the neuroglia fibers. The central portion of the separated fiber will, after a long interval, also degenerate; this is possibly due to functional inactivity, and appears to be more of the nature of an atrophy. Thus in amputations that have occurred in early life, the anterior roots, forming the nerves that supply the amputated limb, become smaller and contain fewer fibers, and there is ultimately some degeneration in their ganglion-cells of the anterior horns. Regeneration of nervous tissue occurs in the invertebrates and possibly among fishes and reptiles, although this is very uncertain. Regeneration of nerve-fibers in the peripheral nervous system occurs in all the higher animals, including man. After the nerve-trunk has been cut, the peripheral ends of the axis-cylinder of the central portion of the nerve become swollen and split up into very fine fibrillæ. These grow in various directions, and, if they unite with the distal portion of the nerve, will serve it as a skeleton, and one of them, at least, will grow toward the periphery, ultimately forming new nerve-fibers. These changes occur in both sensory and motor fibers. (See section upon the Regeneration of the Peripheral Nerves.)

Nerve-cell and fiber degenerations may be produced by endogenous toxins, such as those of uremia, or by the poisons of bacteria and protozoal diseases, and from exogenous poisons, such as lead and alcohol. It is probable that the changes vary with the cause in the early stages, but they are so seldom seen that it is difficult to be certain. The changes seem to take the form of chromatolysis and fatty degeneration in nerve-cells and granular or fatty change in the axis-cylinder and myelin-sheath.

Disturbance of nutrition, either acting locally upon a terminal part of a nerve or by affecting the central cell, will cause degeneration, usually tending to travel toward the controlling ganglion-cell. Fatigue may cause degeneration of a nerve, but it seems that this is due to some primary change in the ganglion-cell.

The **neuroglia** of the nervous system may proliferate or undergo softening, the former change producing various forms of sclerosis or gliosis. Sclerosis of the brain may be either diffuse or circumscribed,

and the latter is again subdivided into the hypertrophic and atrophic forms.

Diffuse sclerosis of the brain never involves all parts equally. To a certain extent it is normal in old age, and is usually found to be limited to the most superficial portion of the cortex beneath the pia, or else to the layer of the gray substance adjacent to the white matter. The neuroglia tissue in either situation appears to be composed of rather coarser fibers than normally, forming either wavy bands or a coarse network. Macroscopically the brains exhibit only slight alteration. The consistency may, on account of other senile changes, be even slightly reduced; the gray matter is usually narrower than normal; the pia mater is generally firmly adherent, but not invariably. This condition sometimes occurs in connection with other diseases, as epilepsy, or may be congenital.

Disseminated sclerosis is sometimes only slight in extent. It may occur in the brains of epileptics, of criminals, of old persons, and of idiots. Small sclerotic foci are usually found at the junction of the gray and white matter, more often in the former than in the latter. The neuroglia tissue forms a coarse, irregular network; as a rule, it is unusually vascular and without any or only a few true nervous elements. These areas may be detected by the naked eye, when large enough, by the fact that they are paler than the surrounding tissue and often slightly sunken. If the process is more extensive and involves the whole thickness of one or more gyri, it gives rise either to an atrophic or hypertrophic form, or both may coexist in the same brain. The external appearance in these cases is characteristic and cannot be mistaken for any other process.

In the *atrophic form* the gyri are reduced perhaps to the thickness of a lead-pencil, they are pale, firm, slightly granular upon the surface and the pia mater may occasionally be slightly adherent. Section through one of these convolutions shows that the cortex is considerably thinner and has a tendency to retract. The white substance is also involved, but apparently less severely. The extent of the process is very variable, one or two convolutions only being affected, or perhaps, as in several reported cases of epilepsy, only the cornua ammonis. Sometimes a number of convolutions are affected, and in the majority of these cases there is some tendency to an irregularly symmetrical distribution. Microscopically these lesions show marked hyperplasia of the neuroglia tissue—that is, increased number of neuroglia cells and coarseness of the neuroglia fibers, which form coarser meshes than normal. Many of the neuroglia cells are swollen, the nuclei are enlarged, pale, and the outlines of the cells are irregular. The nervous elements may appear to be more thickly placed and somewhat irregularly distributed, and the protoplasmic processes of the ganglion-cells are often tortuous. More frequently they are considerably diminished in number or else entirely absent. The myelinated fibers are always decreased, particularly the tangential fibers of the cortex. The vessels are more numerous than usual and often show wide perivascular spaces filled with

fibrous tissue. In the most advanced areas, however, the vessels may be entirely absent. Corpora amylacea or other products of nerve degeneration are sometimes found. These changes are found in epilepsy and idiocy, and when the lesions occur in the motor region are always associated with motor disturbances.

In the *hypertrophic nodular form*, the brain, as a whole, is usually somewhat enlarged, and nodules are found in the cerebral cortex that project from the surface and are much harder than the surrounding substance. The larger ones are often slightly umbilicated. The surface of these nodules is often granular. The microscopical changes are similar to those found in atrophic sclerosis, with the exception that the excess of neuroglia tissue is much more pronounced. In these brains there are often sclerotic areas beneath the ependyma of the ventricles, the lateral ventricles being more frequently affected than the third or fourth. These nodules are small, round, and very hard. Microscopically, they are found to consist of neuroglia fibers arranged in a somewhat concentric manner. They may be vascular or entirely deprived of blood-vessels, and sometimes contain chalky deposits or masses of hyaloid material. As in all destructive lesions of the central nervous system, secondary degenerations may occur, but they are far less common than would be suspected from the apparent extent of the degenerative processes. These forms of congenital sclerosis probably commence after the seventh month of fetal life, because, as Kundrat has pointed out, the arrangement of the convolutions is rarely disturbed. They have been ascribed to syphilis, to inflammatory change, to congestion of the lymphatic system, and to something akin to tumor formation. The absence of round-cell infiltration, and the fact that the pia is rarely adherent, even when the sclerosis takes place in the most superficial layers of the cortex, would seem to exclude inflammatory causation. Neuroglial proliferation occurs about gumma, but there is no ground for believing that all other forms are also due to syphilis. The dilatation of the perivascular spaces is favorable to the theory of congestion of the lymphatic system. This, however, is probably secondary. It is no explanation for this process to say it belongs to the tumors, but at present it appears impossible to give a more satisfactory etiology. Softening of the neuroglia is a part of all processes of softening in the brain, which are described in connection with thrombosis and embolism.

THE BLOOD-VESSELS

The arteries of the brain may be divided into two groups, those nourishing the cortex and those nourishing the basal ganglia. The former are the ramifications of the terminal branches of the circle of Willis; the latter arise directly from the main vessels of the base of the brain.

Arteriosclerosis.—The changes that occur in the arteries are those ordinarily occurring in the vessels of the other parts of the body, atheroma of the arteries of the base of the brain being perhaps more

frequent than of the arteries of other organs. These atheromatous changes usually lead to calcareous infiltration, and in old age often the entire circle of Willis is composed of typical pipe-stem arteries. When the process is less extensive, the calcareous infiltration is most apt to affect the two internal carotids, the middle cerebrals, and the basilar artery.

Hyaline degeneration may also occur. It is of two kinds: that which forms simply the early stage of arterial sclerosis, and another process that is apparently independent of this and occurs as a diffuse degeneration of the intima and media. This latter form is frequently found in the brains of idiots even during early life. Occasionally it is also found in senile brains, but in these cases is not so certainly independent of arterial sclerosis. Amyloid change of the blood-vessels may occur as a part of general amyloid disease, but is not especially common in the brain.

Colloid Degeneration.—A rare form of degeneration has been spoken of as colloid, although the material discovered in the blood-vessels seems more akin to that of hyaline degeneration. In this process the adventitia and the media are greatly thickened as a result of their infiltration with a homogeneous translucent material, which may be deposited irregularly in masses or else cause a diffuse thickening of the wall. The masses project into the surrounding nervous tissue, and may sometimes be detached, forming then independent clumps that are not unlike the so-called amylaceous bodies, although they fail to give all the characteristic amyloid reactions. This condition is usually associated with profound disturbances of the intellect, and may be associated with clinical symptoms that resemble those of general paresis.

Syphilis frequently causes thickening of the intima or *endarteritis*, which may be due either to the usual round-cell infiltration or to the formation of fibrous tissue. Tuberculosis may also cause *endarteritis*. This form is most frequently associated with tuberculous meningitis, and therefore the basilar artery is the one commonly affected.

Aneurysms may occur in any of the components of the circle of Willis. The basilar artery is the one most frequently involved, usually just at its posterior extremity. Large aneurysms of the arteries of the brain proper, or of the arteries of the vertex, are exceedingly rare. A saccular aneurysm, as large as a cherry, springing from the anterior communicating artery, was observed at the Philadelphia Hospital. *Miliary aneurysms* of the brain are, on account of their relation to cerebral hemorrhage, the most important form of vascular disease in the brain (see Fig. 215). These aneurysms may be ectatic or saccular. The ectatic forms are usually fusiform in shape, and often consist of but a single coat of the vessel wall; that is to say, they are merely endothelium surrounded by a thin layer of fibrous tissue. The saccular aneurysms are usually somewhat larger; they appear as bulbous swellings on one side of the vessel, connecting with the lumen by narrow openings. They may consist of a single wall, as in the fusiform type,

the most common variety, or of the intima or adventitia, with a considerable amount of fibrous thickening. Occasionally the fusiform aneurysms may exhibit distinct atheromatous change, but even in these instances the media is atrophic, and they are certainly exceptional. It is doubtful whether arteriosclerosis is of much importance in connection with the formation of these aneurysms, and it is certain that in the majority of cases the first change in the vessel is a fatty degeneration of the media. This leads to local weakening of the wall and to consequent distention—a change that is favored by the considerable degree of pressure to which the arteries springing from the middle cerebral or from the beginning of the basilar artery are subjected. According to some authors, these aneurysms are to be regarded as herniæ of the intima, really the result of atrophy of the muscularis; nevertheless, they are more frequent in the old, and certainly in the majority of cases, in which they are found the arteries of the base are distinctly atheromatous. The formation of thrombi in miliary aneurysms is exceptional.

CIRCULATORY DISTURBANCES

Circulatory disturbances in the brain differ from those in other parts of the body on account of the presence of a rigid bony capsule (the skull), which prevents any increase or decrease in the size of the contained viscus. Variations in the quantity of blood, however, do take place in adults, and are rendered possible, first, by the elasticity of the nervous substance itself, which is capable of undergoing a slight degree of compression or extension, and, second, by the free communication of the subarachnoid spaces of the brain and cord and the ventricular cavities, so that the cerebrospinal fluid may be in greater or less quantity in the cavity of the skull or in the spinal canal, and thus permit variation in the amount of blood in either region. Local congestion or anemia may occur as a result of local disturbances, but the free anastomosis of the arteries of the circle of Willis provides such facility in equalizing the amount of blood flowing to the different parts of the brain that neither is often found in general conditions. In very young children these mechanical restrictions do not obtain, because the fibrous union between the bones of the skull permits of very considerable changes in the size of the cranial cavity.

Acute anemia of the brain may occur as a result of severe hemorrhage, or of hyperemia in other parts of the body, particularly the pulmonary and abdominal organs, and it has been supposed to exist in fainting, during hysterical crises, and in sleep. It must be admitted, however, that certain proof of its existence either as a cause or effect of these conditions is lacking. Microscopically, the brain is usually pale and firm. There is little or no tendency on the part of the small venules of the white substance to bleed upon cross-section, and the gray matter is distinctly paler, so that the distinction between it and the medullary substance is not so distinct as is the case in normal tissue. Sometimes in these conditions there is overfilling of the veins of the pia as a result of the shrinking of the brain. The changes in the *func-*

tions of the brain tissue ascribed to this condition are partly irritative, partly paralytic. They are very indefinite.

Chronic anemia of the brain may occur in severe cachectic conditions, such as progressive pernicious anemia, lead- or malarial poisoning. It may also be the result, though less frequently, of atheroma of the cerebral arteries, with a general narrowing of their lumina. The brain is small, the consistency varies according to the duration and nature of the process, being at first hard, later, probably as a result of degenerative changes, slightly softer than normal. The ventricles are not dilated at first, but the convolutions are shrunken and the sulci are wider as a result of the diminution in size of the brain as a whole. The substance of the brain is pale, and often seems slightly moister than normal. Local anemia may occur as a result of thrombosis or embolism, and usually leads to softening.

Active hyperemia of the brain is nearly always associated with inflammatory or toxic conditions. It is perhaps most frequent in association with meningitis or encephalitis. It is always found after death from sunstroke, acute delirium, cholera, and hydrophobia, as well as, occasionally, after death from infectious disease. It may be local or general.

Local hyperemia is usually associated with meningitis, and may be limited to the superficial layer of the cortex beneath the meningitic areas. The affected parts are darker than normal and may even contain punctiform hemorrhages. Microscopically the blood-vessels are found to be dilated, and there is more or less degeneration of the adjacent nerve substance, according to the duration of the process. Local hyperemia may also occur after thrombosis, and leads to red softening of the nerve tissue.

General Active Hyperemia.—The brain is darker and larger and its consistency is softer. The blood-vessels of the pia are injected. The gray matter is darker and, as in the local form, may contain minute hemorrhagic foci. The white matter is moist; its color is rarely altered, but as soon as the section is made it is covered with small red spots, representing hemorrhages from the veins and capillaries. These may be readily distinguished from interstitial hemorrhages by allowing a little water to flow over the surface of the section, when they will disappear. Microscopically, aside from the distention of the vessels with blood, pronounced degenerative changes are rarely found, excepting in those cases resulting from infectious diseases. In these the alterations commonly associated with severe toxemia are present, but are to be considered as complications and not as the result of the circulatory disturbances.

Occasionally, in acute infectious diseases such as typhoid fever, a condition occurs in which there is evidently excessive irritation of the central substance, manifested by symptoms not unlike those of meningitis. Postmortem in these cases the only changes found are hyperemia of the brain. Even microscopically no distinct inflammatory lesions can be discovered. This condition has been termed *meningismus*.

Passive hyperemia may be associated with valvular heart disease or chronic lung disease, or it may be caused by tumors in the neck pressing upon the jugular veins, or by intracranial conditions. Of the latter, the most important are brain tumors compressing the veins, whilst the arteries still continue to convey blood and thus cause increase of the cranial contents. When the tumors press upon the veins of Galen passive hyperemia and distention of the ventricles are particularly common. Passive hyperemia may also be caused by thrombosis of the dural sinuses. In acute passive congestion the veins of the dura are widely distended; the subarachnoid space is moist; the brain seems to be slightly larger, softer and moister than normal. The gray matter is of a slaty color. The white matter may have a faint bluish tinge, and its capillaries and ventricles bleed freely upon cross-section. The ventricles may not be larger, but appear to contain fluid under pressure that wells forth when they are opened.

Edema of the brain nearly always occurs when passive hyperemia persists, and also occurs in cases of chronic alcoholism. It is characterized by the distention of the subarachnoid space with liquid, so that the convolutions are no longer distinct and the surface of the brain has a clear or pearly appearance. The arachnoid is usually thicker, particularly along the sulci. The fluid is clear, or perhaps very slightly turbid; it has a higher specific gravity than the cerebrospinal liquid, coagulates upon boiling, and is usually found to contain numerous cellular elements. A microscopical examination of the brain and its membranes shows marked distention of the subarachnoid space, which is usually divided into irregular spaces by delicate fibrous bands. The endothelial cells appear to have undergone some proliferation, and in many places have desquamated and lie free in the areolar spaces. Around the blood-vessels there is occasionally slight extravasation of round cells, which are usually mononuclear and resemble lymphocytes, and indicate an inflammatory reaction to the long-continued pressure. The arachnoid is usually thicker, the thickening being almost exclusively fibrous in nature. The pia is slightly thicker, and sometimes may be seen to have coalesced with the superficial layer of the cortex. In the brain substance the perivascular spaces are distended, the neuroglial meshwork is coarser than normal, and there may be slight evidences of degeneration in the cells.

Local edema of the brain, the so-called *apoplexia serosa*, is occasionally found in the neighborhood of areas of softening. In cases of acute hydrocephalus this serous infiltration sometimes occurs in the neighboring internal capsules, and may even lead to transient hemiplegia.

Cerebral hemorrhage occurs in two varieties: the so-called punctate form and massive hemorrhage.

Punctate hemorrhages are due to some alteration of the vessel walls or of the degree of blood-pressure, causing extravasation of blood into the surrounding tissues. The commonest causes are mania, convulsions and encephalitis, and severe infections. The hemorrhages are

small, often microscopical, and are by far most common in the gray matter, especially in the cortex. The principal causes are hyperemia, particularly if associated with inflammatory conditions of the brain, and convulsions. The wall of the blood-vessel may be diseased, but does not always show solution of continuity, or the hemorrhage may burrow along beside the vessel like a dissecting aneurysm, but yet free against the nerve tissue. The blood-pigment is more or less altered, according to the length of time that has elapsed between the occurrence of the hemorrhages and the examination of the tissues. The nervous tissue immediately involved is edematous, and there is usually some proliferation of the neuroglia cells in the vicinity. Such hemorrhages, of course, may heal without leaving any trace, for the secondary degenerations that may possibly be caused are too slight to be detected.

Massive hemorrhages usually occur from the branches of the middle cerebral artery—that is, from the vessels most frequently the seat of miliary aneurysms. The arteries commonly involved are the lenticulostriate and lenticulothalamic branches of the middle cerebral vessel, and the hemorrhage occurs in the internal capsule. These vessels have no anastomoses. Hemorrhages may occur in the centrum ovale or the pons, or, in fact, in almost any portion of the central nervous system. The attack is precipitated by a sudden strain, of physical or mental nature, upon a diseased vessel or upon an aneurysm. The blood usually collects in the form of an irregular dark-red mass that in recent cases rapidly becomes bright red upon exposure to the air. The size of the hemorrhagic area naturally varies with its location and the amount of blood extravasated. Its outline is exceedingly irregular, and almost always separate small hemorrhagic foci are found in the surrounding tissue. According to the density of the tissue, the blood is more or less dispersed. Thus, in the white matter the extravasation is usually more diffuse than in the gray, where hematomata are exceedingly apt to form. The substance of the brain is soon softened. Its structure is usually entirely lost, although it may be possible in recent cases to recognize the presence of altered cells and nerve-fibers. The neuroglia usually shares in this softening, but if the hemorrhage is not extensive, it may remain and form a sort of skeleton for the blood-clot; the tissue then is not nearly so soft, and the surface upon section usually is smooth. If the hemorrhage occurs in the internal capsule, as is usually the case, and is at all extensive, the blood may creep inward toward the ventricle, into which it may rupture, filling the lateral ventricle and sometimes extending into the third ventricle and into the lateral ventricle on the other side (Fig. 427). Occasionally, in exceedingly severe cases, almost the whole of one of the hemispheres may be destroyed; this is usually associated with sudden death, and is known as the foudroyant form of apoplexy. The softened brain substance can usually be readily washed away by a current of water, leaving the blood-vessels, which should then be examined with a low power for the presence of miliary aneurysms. If the patient survives his first attack, rapid alterations begin to take place in the diseased tissue. The throm-

bus contracts, causing edema in the surrounding tissues. A capsule of delicate fibrous tissue may even be formed about it. The small hemorrhages in the surrounding tissue are absorbed. The color of the softened region becomes dark brown, and it may either go on to complete liquefaction, with the subsequent absorption of the pigment and the formation of a cyst, or else be gradually entirely absorbed, leaving a pigmented scar. The walls of the cysts are usually discolored by pigment, and in the neighborhood pigment-granules and compound granular cells are found in great numbers. These old hemorrhagic cysts are very difficult to distinguish from those produced by other forms of softening. Often the contents are slightly discolored, the walls are dense and somewhat sclerotic in nature, and may contain crystals of hematoidin. It is somewhat doubtful whether the walls are composed of neuroglial tissue or of true fibrous connective tissue derived



Fig. 427.—Hemorrhage into the internal capsule and the caudate and lenticular nucleus of the right cerebral hemisphere (from Bollinger).

from the blood-vessels. It is certain, however, that shortly after extravasation of the blood, hyperplasia of the neuroglia in the immediate vicinity takes place. This may occur very rapidly, so that in the course of a few days new neuroglia fibers may be seen pushing their way into the hemorrhagic area from the collection of neuroglia cells in the nearest healthy tissue. After healing has taken place the hemisphere is usually reduced in size. This reduction is not merely equivalent to the amount of nerve tissue that has been destroyed, but represents also the secondary degeneration that occurs in the nerve-fibers whose course has been interrupted by the lesion. This is both ascending and descending, and frequently causes sclerosis that involves not only the brain, but extends throughout the pyramidal columns.

Pathological Physiology.—The *disturbances in the functions* of the central nervous system produced by hemorrhage are among the most interesting in the domain of nervous physiology. At the time of the rupture of the vessel the patient almost invariably becomes suddenly unconscious and falls, the face is flushed, and there may be convulsive movements. This is termed *apoplexy*. The period of unconsciousness may persist for a longer or shorter interval, according to the amount of hemorrhage that has taken place. If the patient recovers, the subsequent changes depend upon the situation of the hemorrhage and the extent of the destruction of nervous tissue that has taken place. As will readily be seen from the description of the pyramidal tract, lesion in any part of its course above the first cervical segment produces paralysis of the opposite side of the body; if above the middle of the pons, paralysis of the lower portion of the face on the opposite side is also produced; if below this point, paralysis of the same side. Monoplegias are likely to occur if only a small portion of the fan-like projection fibers of the pyramidal tract is involved, such as would be produced by a lesion in the cortex or in the centrum ovale. In all these cases only the superior motor neuron is affected, and in consequence, either because some inhibitory influence is removed or because the lower motor neurons are irritated by the products of degeneration, a condition of spasticity arises in the muscles. Subsequently, their nutrition is impaired and they contract. An interesting series of disturbances is produced by lesions occurring in those portions of the cortex that have to do with manifestations of speech, either receptive or motor. If the former are involved, we speak of it as amnesia; if the latter, as aphasia. Lesions of the optic tract posterior to the chiasm cause hemianopsia.

Secondary Degeneration after Hemorrhages.—As a result of hemorrhage into the brain substance with destruction of tissue secondary degenerations appear, which, of course, are systemic and follow the direction in which the nerve-fibers convey impulses. Of these the most important are the degenerations of the pyramidal tract, of the optic tract, and of the projection fibers from the temporosphenoid lobes. A discussion of this subject involves consideration of the anatomy of the brain more than of the pathology, and only the most important details can be given here. Degeneration of the *pyramidal tract* may be sharply circumscribed if the focal lesion is situated in the cortex or the centrum ovale. In this case a slender band of degenerated fibers may be traced along the pyramidal tract. This is only possible, however, if the lesion is sufficiently recent to permit the employment of Marchi's staining method, for otherwise it is impossible to recognize a small number of degenerated fibers in the midst of a group of healthy ones. As the hemorrhage usually takes place from the lenticulo-caudate artery and involves the complete destruction of the pyramidal fibers in the internal capsule, it not infrequently happens that the entire pyramidal column of one side undergoes secondary degeneration. Interruption of the fibers of the *optic radiation*, or destruction of the primary optic centers, causes secondary degeneration which does not,

however, appear as promptly as in the motor fibers. There is degeneration in the external geniculate body, in the pulvinar, and in the anterior corpus quadrigeminus of the same side. Ultimately, degeneration may also occur in the optic nerves. Destruction of the second and third temporal lobes, or of the projection fibers arising from them, causes secondary degeneration in the posterior limb of the internal capsule. The fibers appear to extend into the thalamus, and also into the crusta. Destruction of other parts of the brain cortex causes degeneration, which seems to affect chiefly the projection fibers. Extensive hemorrhages into the cerebellum usually cause death, as a result of pressure upon the medulla. If, however, the patient survive, and if the nucleus dentatus be particularly involved, there is degeneration of the superior cerebellar peduncle, which may be traced as far as the red nucleus in the tegmentum. All these secondary degenerations are quite typical in character. They appear about the ninth day, the first changes being the degeneration of the myelin-sheath. This is followed by the appearance of compound granular cells and hyperplasia of the neuroglia, and later corpora amylacea may sometimes be found. Ultimately nothing but the neuroglia remains, and this is composed of coarser fibers than are found in normal nervous tissue. Occasionally, nerve-fibers without myelin-sheaths are found traversing the sclerotic tissue.

Thrombosis and embolism of the vessels of the brain are due to causes that produce the same processes in other parts of the body. Embolism will produce attacks of apoplexy like massive hemorrhage; but thrombosis, while causing paralysis and nerve-tract degeneration, does so much more slowly. Thrombosis may occur anywhere. It is perhaps more frequent in the basilar artery than in other situations, but this rule is by no means certainly established. The causes are, of course, chiefly atheroma of the vessels or syphilitic endarteritis. Embolism, on the other hand, usually occurs in the artery of the Sylvian fissure. Perhaps 80 per cent. of all cases occur in this situation. This frequency is due to the fact that the course of the blood is direct from the heart to this vessel, and its importance lies in the fact that it is an end artery and, therefore, its occlusion is most apt to lead to cerebral necrosis. Less frequently an embolus will lodge in the anterior cerebral, but it is probably extremely rare for an embolus to travel along the posterior communicating artery and lodge in the posterior cerebral. A more frequent route of embolism into the latter artery is along the vertebrals to the basilar. Embolism in the basilar artery can, of course, never occur, as its lumen is greater than that of either of the branches from which it receives blood. A saddle embolus may occasionally lodge at its bifurcation and give rise to local thrombosis. Sometimes the two processes occur simultaneously—that is, fragments of a parietal thrombus in one of the vessels may be washed off into the blood-stream and be carried along the artery until they occlude its lumen or that of one of its branches. The results of embolism or thrombosis may be either infarction, or, if the obstruction takes place slowly, as in thrombosis, it then being possible for a collateral circulation to be

established, there may be no changes or only temporary results. The functional disturbances are very similar to those of hemorrhage. As, however, the lesions frequently occur very slowly, the sudden shock may not occur and the paralysis may supervene without any period of unconsciousness.

Infarction of the brain usually leads very rapidly to cerebral softening (*encephalomalacia*). It has been usual to describe three forms—red, yellow, and white—which, while frequently pure in form, are at times but stages of the same process, and they do not constitute separate pathological entities.

Red softening corresponds very closely to the hemorrhagic infarct. It consists of a serous infiltration of the tissue, the extravasated liquid containing numerous red corpuscles. The same theories that have been suggested for the explanation of a hemorrhagic infarct have been used to explain its occurrence.

Yellow softening is really only the red softening after more complete liquefaction has taken place and most of the pigment has been absorbed.

White softening is a term applied to two very different conditions. The first corresponds to the anemic infarct, and appears very shortly after the occlusions of the vessels. The second is a late stage of any form of softening, and is characterized by the occurrence of an excessive amount of fat in the softened area, producing an emulsion. The white color becomes even more pronounced after the fat has been absorbed, and the lesion is represented only by coarse neuroglia fibers. Macroscopically, the earliest changes usually appear toward the end of the first twenty-four hours. The brain substance in the softened area is swollen, softer, and somewhat mottled in appearance and may even exhibit small punctiform hemorrhages. The lesion is not sharply delimited, but fades gradually into the surrounding tissues.

If a large artery has been obstructed, a considerable portion of the brain may be softened and there will be a large extravasation of blood. In this case the parts of the brain showing the greatest alteration are those nearest the periphery of the distribution of the obstructed vessel, and these changes may even occur without complete obstruction if the general circulation is impaired, as in valvular heart disease, or as a result of profound general anemia. As the process continues, more and more blood is extravasated into the tissue, giving it a bright-red appearance. The lesion by this time becomes more circumscribed, although the surrounding tissue may be somewhat softened, and, as in the case of cerebral hemorrhage, may contain punctiform hemorrhages. As soon as the demarcation is complete the brain tissue becomes rapidly softer, probably as a result of the obstruction of the lymph-channels by which the nutritive fluids enter. The nerve-cells undergo almost complete degeneration; they lose their axis-cylinders and their tinctability, and may either disappear completely or be no longer recognizable. The myelin-sheaths undergo a fatty degeneration, in which the nerve-fibers soon take part. The whole tissue is filled with compound granular cells. The neuroglia fibers may also become softened and, to a large extent,

liquefied, although they persist longer than the other elements. The wall of what has now become a cyst is composed of the surrounding neuroglial tissue, newly formed capillaries, and nervous tissue in an advanced stage of degeneration. The blood-vessels, however, usually persist for some time, although they are filled with thrombi and form an irregular spongy network in the lesion.

When organization commences the blood-pigment gradually disappears, and the material changes from a brownish, turbid fluid to a lighter yellow mass, often irregularly surrounded by deeply pigmented cells. Later, complete contraction takes place, and a scar, composed chiefly of neuroglia tissue, but also containing some fibrous connective tissue that has developed from the walls of the blood-vessels, is left. It is, of course, clear that red softening is more frequent in the vascular parts of the brain, and white softening in those regions that are poorly supplied with blood, particularly in the white substance of the cerebrum. The areas are rarely as well circumscribed as those of red softening, and often do not lead to complete destruction of the tissue, causing only numerous adjacent minute focal lesions, the so-called *état criblé*.

A peculiar form of softening occurs in the cortex of the brain. It is usually found in lesions that have existed for some time. The area is yellow, depressed, and somewhat circumscribed. The pia mater over and around the lesion is somewhat thickened, and often the surrounding blood-vessels show thickening of the walls, although this latter change is probably the cause and not the result of the gross lesion. These are the so-called *plaques jaunes* of French writers, and if extensive they lead to considerable retraction of the brain substance and to the formation of collections of liquid in the subarachnoid space (*hydrops e vacuo*; *external hydrocephalus*).

Areas of softening, probably due to capillary thrombosis, are frequently found in children suffering from tuberculous meningitis. They may also occur in other forms of meningitis, and also in encephalitis, although in these latter conditions the presence of pyogenic micro-organisms in the emboli lead to somewhat different changes, which will be described in connection with encephalitis. Traumatism may also cause softening, often multiple in character, and not necessarily situated directly beneath the point of injury. As a result of the destruction of tissue, secondary degenerations occur that differ in no respect from those following hemorrhage.

INFLAMMATION

Encephalitis, or inflammation of the brain substance, is probably not essentially different from inflammation of the other tissues in the body. The nature of nervous tissue, however, and the peculiar reaction that it manifests to various injurious agencies, render this subject one of the most doubtful and difficult in the pathology of the central nervous system. The various forms may be classified, first, as acute and chronic. The important forms of acute encephalitis are the

parenchymatous, the simple, the hemorrhagic, and the suppurative. Chronic encephalitis may take the form either of sclerosis or of scar-formation, the latter really only a modification of the former. Acute encephalitis may be considered to be disseminated or focal. No case has been recorded in which there was generalized inflammatory change in the brain, and it is inconceivable that such a condition should be compatible with life.

Acute parenchymatous encephalitis is rather a form of degeneration than of specific inflammation. Changes in the nerve-cells without associated vascular phenomena have been observed and described in a number of intoxications, either the result of direct poisoning or infection. More or less extensive changes have been recorded as a result of poisoning by alcohol, arsenic, and other poisonous substances. Of the infectious diseases that have been studied, the most important are diphtheria, tetanus, leprosy, and hydrophobia. The changes differ somewhat in nature, and, of course, in the different cases, considerably in degree. The most important and typical have been already described in the section upon degeneration of the nerve-cells. These forms of encephalitis, if the name may properly be applied to them, may lead to death, but recovery even from the advanced stages is not impossible. Neither the brain nor the cord in these cases exhibits any macroscopical changes, excepting, perhaps, passive congestion of the membranes when death was preceded by violent convulsions, as in tetanus.

Simple acute focal encephalitis is characterized by the development, in various parts of the brain, of areas of softening that may range from a millimeter to several centimeters in diameter. They are usually irregular in size and very indistinctly separated from the surrounding tissue. The most common situations are the region of the third and fourth ventricles and the aqueduct of Sylvius. The gray matter is more often involved than the white. Polioencephalitis is a localized cerebritis of the basal ganglia bulb or pons, or all of these, affecting chiefly the motor ganglia, with cytolysis, and some cellular infiltration around them and about the blood-vessels. It is more extensively considered under Poliomyelitis.

Etiology.—The cause is probably in all cases the presence of infection in the body, such as influenza, typhoid fever, or septicemia. Authors, whose opinions we must respect, have, however, described encephalitis as the result of simple concussion of the brain, or of various forms of poisoning, such as lead. The difficulty in the latter group of cases is due to the close resemblance between encephalomalacia and encephalitis. Collections of round cells, with slight degenerative changes in the nervous system, have been described in chorea, and have been supposed to represent the subacute or chronic form of encephalitis. The observations are, however, at present insufficient to establish this point. References will be made again to it under the heading of Chronic Encephalitis.

Pathological Anatomy.—The two most important changes are those in the color and consistency. The former is usually slightly

darker than normal, but may, if, as is not unfrequently the case, extensive hemorrhage has occurred, become a bright red, resembling, upon inspection, an area of hemorrhage, or perhaps more closely, an area of red softening. The consistency is always decreased, probably as a result of serous infiltration. Often the diseased area projects slightly from the surface of the section. Microscopically, the characteristic change is the perivascular round-cell infiltration. This usually involves the majority of vessels in the lesion, and may also be found in regions of the brain in which softening has not already commenced. Usually there is the characteristic inflammatory congestion, the blood-vessels, particularly the small capillaries, being sometimes greatly distended and packed with red blood-cells. In some cases thrombi have formed. Hemorrhages are exceedingly frequent; these are sometimes punctiform and sometimes diffuse extravasations into the tissue. Often they appear to represent ruptured capillaries, and produce a peculiar speckled appearance on the surface of section. In the early stages the cellular exudate is chiefly composed of polynuclear leukocytes. If the process is more advanced, these may exhibit more or less degenerative changes. Later they are replaced by mononuclear cells, probably representing proliferation of the endothelial cells, and perhaps of the neuroglia cells. The ganglion-cells in the inflammatory region undergo rapid degeneration, usually passing through various stages of chromatolysis, until they are reduced to little colorless vesicles of irregular form. The nerve-fibers also degenerate; the myelin forms fatty droplets; the axis-cylinders at first swell and then share in the granular disintegration. In the midst of the focus the neuroglia ordinarily shares in the softening. At the periphery there is usually a noticeable proliferation of the neuroglia cells and the formation of a coarse, thick network of neuroglia fibers. Of course, these changes are not found about very early lesions. In the earliest stages compound granule cells are usually absent; later they may appear in considerable numbers, but their presence is by no means sufficient to indicate the existence of an acute or chronic inflammatory process. Disappearance of the tangential fibers in the cortex, in lesions situated in this area, have also been described. Ordinarily, in these forms of encephalitis, the rest of the brain exhibits no macroscopical changes, and often none can be detected by the microscope. The membranes are smooth, the vessels of normal elasticity, and not surrounded by a round-cell infiltration. Complete resolution may perhaps occur; of course, this can only be supposed from the clinical symptoms of the disease, there being no definite experimental or pathological evidence to support it.

The focal lesions may undergo softening and lead ultimately to scar-formation, and if they are extensive there will be considerable atrophy of the affected part of the brain. The great majority of cases, however, in all probability terminate fatally. The nature of the process is generally accepted to be primarily vascular, the secondary changes being the result of alteration in the nutrition of the surrounding part.

Suppurative encephalitis has already been in part described in con-

nection with purulent meningitis. In that condition, the pyogenic emboli appear to enter the brain substance along the lymphatics that dip into it from the pia. They are usually small, not circumscribed, and more apt to be found in the gray matter of the cortex, particularly near the base of the brain and in the structures adjacent to the ventricles, than in the white substance. Occasionally larger collections, forming rather ill-defined abscesses, are found. In a brain that one of us removed at autopsy the changes in the pia arachnoid were slight and were limited to a small area over the motor region for the leg on the left side, but beneath this there was an extensive area of purulent infiltration of the brain substance, not sharply circumscribed.

Abscess of the brain is a condition characterized by the presence in the brain substance of one or more cavities containing pus. The usual cause is suppurative bone disease, particularly that resulting from otitis media. This condition may, however, occur in general pyemia as a result of metastasis from some neighboring or remote focus of suppuration. Suppuration may also occur in the course of pneumonia, or in chronic suppurative diseases of the lungs, such as fetid bronchitis. Direct infection of the brain, either experimentally or as a result of wounds penetrating the skull, has also been observed. In many of these cases the nature of the transmission is clear; thus the abscess resulting from otitis media, disease of the ethmoidal sinuses, or from direct inoculation, is usually situated in the immediate neighborhood of the original focus. Abscess secondary to pulmonary disease is usually found at the base of the cerebral hemispheres, and is probably transmitted along the retropharyngeal lymphatics. Abscess due to injury without penetration of the skull has occasionally been recorded; sometimes it is found in the contused area, sometimes on the opposite side of the brain. The micro-organisms that have been found in the pus include practically all the pyogenic forms. The most frequent are, perhaps, the staphylococcus, the streptococcus, and the pneumococcus. Occasionally the actinomyces, the *Bacillus pyocyaneus*, and the *Mycobacterium tuberculosis* have been found, the latter in cases that were apparently acute abscesses of the brain, and not softened solitary tubercles.

Statistical studies of the literature show that in about two-thirds of all cases the cerebrum is the seat of the lesion; in the remaining third it is chiefly the cerebellum. This distribution does not, of course, apply to the disseminated forms of purulent encephalitis. Solitary abscesses are usually the result of embolism or extension from the bones. They may be small or of considerable size, and one is on record from which 400 c.c. of pus were removed. They may be either surrounded by softened brain substance or distinctly encapsulated. The latter condition usually occurs if they have lasted any length of time—that is, three or four weeks; although cases are on record in which a distinct wall did not develop about an abscess that had existed for several months. The contents of the cavity are pus and detritus, and in it may frequently be found thrombosed blood-vessels. The surrounding brain

tissue is usually undergoing softening. It may be either white, or, as a result of hemorrhagic extravasation, red in color. The abscesses usually spread more or less gradually; that is to say, there is probably no tendency to heal spontaneously. If large, they cause considerable intracranial pressure, which is indicated by the flattening of the convolutions or bulging of the brain after the skull has been trephined. Those due to punctured wounds are usually associated with meningitis. Those due to caries must also be associated with inflammatory changes in the meninges, and not unfrequently there is thrombosis of the cerebral sinuses. Microscopically, we find the ordinary characteristics of pus. The wall or periphery is usually undergoing fatty degeneration, and there is a considerable accumulation of round cells in the surrounding tissue. Metastatic abscesses are usually multiple. A group may be found either in one situation in the brain or they may be very widely distributed. In cases of severe encephalitis more or less pronounced changes may be observed in the ganglion-cells in other parts of the central nervous system.

Primary Acute Hemorrhagic Encephalitis.—Strümpell described under this name a form in which the dura was normal but somewhat dry; the pia injected, the centrum ovale softened, edematous, slightly pinkish or gray, and marked by fine hemorrhagic points. Microscopically there were no granular cells, but drops of myelin and some detritus. There was some hyperemia and cellular infiltration of the pia. The ganglion-cells of the cortex were normal. In the white matter the vessels were distended with blood and surrounded by thick masses of round cells; the perivascular spaces were distended; the neuroglial tissue coarser than normal. In many situations there was bleeding from the capillaries.

Chronic encephalitis may take the form of sclerosis or of scar-formation, which is really but a variety of sclerosis. (See Neuroglia.)

Lobar sclerosis is usually an extensive but sharply circumscribed process affecting the whole or part of one or more lobes of the brain. The involved area is usually considerably diminished in size. The convolutions are smaller, the sulci broader, but, of course, not so deep; the surface is often finely granular, and the pia is adherent. The consistency is greatly increased, the tissue being almost like cartilage. Microscopically there are the same changes found in the other forms—that is, excessive proliferation of the neuroglia, with partial or complete disappearance of the nervous elements. The cause appears to be some vascular disturbance occurring during fetal existence, as the localization nearly always corresponds to the distribution of one of the arteries supplying the brain. If the anterior cerebral artery is affected, the frontal lobe is sclerotic. If the artery of the Sylvian fissure is involved, there will be sclerosis of all the hemisphere, with the exception of a part of the occipital lobe; and if the lesion is situated on the proximal side of the lenticulostriate artery, this part will also be degenerated. If the posterior cerebral artery is occluded, the lesion will be found at the

tip and in the lower half of the occipital lobe. Extensive secondary degeneration always occurs in this form.

Multiple or disseminated sclerosis is a condition characterized by the formation throughout the nervous system of various foci of irregular size and distribution in which the neuroglia is somewhat hyperplastic, the myelin-sheaths more or less degenerated, and the axis-cylinders, as a rule, slightly, if at all, affected. When sclerotic areas affect the white matter of the brain and cord they appear as grayish or grayish-pink areas, which may, if at the surface, be observed through the pia. They resemble the gray matter of the cord too closely to be clearly distinguished from it. Their edges are usually sharp. After hardening in Müller's fluid they appear of a bright yellow color and are exceedingly distinct. The smallest may be only a millimeter in diameter, and the largest may occupy the whole transverse section of the spinal cord or even entire convolutions of the brain. Occasionally sclerotic areas may be found in the nerve-roots. The most important change that is found upon microscopical examination is a thickening of the walls of the blood-vessels, surrounded by a zone of proliferated glia tissue of irregular width and arrangement. The vessels may be thickened by hyaline degeneration, and the productive changes with the degeneration lead to narrowing of the lumen. The perivascular lymphatic space is often filled with cells containing droplets that stain black with osmic acid. Occasionally the vessels appear to be increased in number, although this is possibly due to contraction of the surrounding tissue bringing them more closely together. In the center of the foci the neuroglia cells are not markedly increased; in the periphery, however, they seem to have undergone a distinct hyperplasia. The neuroglia fibers throughout are somewhat thicker and more irregular, and form a large-meshed network. In the midst of the neuroglia compound granular cells and amyloid bodies are often found. If stained by Weigert's method, it is at once evident that the myelin-sheaths have disappeared almost entirely, all the sclerotic areas appearing bright yellow. If the Marchi method be used, however, a certain number of degenerated myelin-sheaths will be found, as a rule, still present. The edge of the sclerotic area does not end as sharply as appears macroscopically, but gradually fades into the healthy tissue. The axis-cylinders, in spite of the destruction of the myelin-sheaths, are nearly always present and apparently normal, a fact which explains the *absence of secondary degeneration beyond the lesions*. In those situations where the hyperplasia of the neuroglia fibers is most pronounced, the axis-cylinders may be swollen or show partial fatty degeneration, or be entirely absent. The ganglion-cells are shrunken and pigmented, and may, in rare cases, completely disappear. In advanced cases of the disease the process resembles more closely a chronic myelitis; the axis-cylinders passing through the lesion may be totally destroyed and secondary degeneration occur. In those cases that have been studied in the early stages of the process perivascular inflammatory changes have been present, and it is about these that the sclerotic areas have

formed. In some cases thrombi have been also detected in the vessels, and many of them show the early stages of hyaline degeneration. For this reason, and because disseminated sclerosis frequently develops after an infectious disease, it is generally accepted that the process is due to infectious embolism. Certain authors, however, hold that the vessels are not the primary origin of the disease, as in many of the sclerotic foci they are perfectly healthy.

General Progressive Paralysis.—Paresis.—There has been much diversity of opinion concerning the true nature of general progressive paralysis. The lesions hitherto described have varied in nature and situation. Nevertheless, there seems to be good reason to accept an infectious origin of the disease, and unquestionably the symptomatology and, to a certain extent, the morbid changes indicate that the brain is the organ chiefly involved.

The etiology is not yet clear, but some assistance has lately been produced by the finding by Noguchi of the *Spirochæta pallida* in the brain of paretics. He has succeeded in showing the presence of these spirals in a goodly proportion of cases, in a few instances in enormous numbers, not only in the brain, but in the cord, especially of tabetics. Clinically, it is difficult in many cases to get a history of syphilis, but this disease is certainly the more important factor in the causation of paresis. It is a disease of any age past adolescence, and has been seen in the very young. The Wassermann test is positive in a vast majority of the cases.

The changes found most frequently are as follows: the dura mater is adherent to the skull; it may be thickened, and often shows upon its under surface the exudate of a hemorrhagic pachymeningitis. The arachnoid is thickened and opaque, particularly along the course of the veins; and in the subarachnoid space there is often a considerable effusion of liquid. The pia mater is thickened and opaque and may or may not be adherent to the cortex; in the latter case the subpial areolar tissue is distended with fluid. Microscopically, there is often found a round-cell infiltration about the blood-vessels; their walls are thickened and show some hyaline degeneration. The fluid in the areolar spaces may be clear, or, as is more commonly the case, it is viscid and even colloid in nature. The gross appearance of the brain is frequently considerably altered. The convolutions are flattened; the sulci broader than normal; the consistency of the brain is slightly increased; the cortex is usually pale and greatly reduced in thickness. The white matter may appear to be slightly looser in texture, but ordinarily presents no change. Microscopically, the blood-vessels in the cortex have thickened walls, and occasionally one is found with a completely obliterated lumen. There is usually distention of the perivascular spaces, which may be filled with round cells and various products of degeneration, such as pigment granules. The glia-cells are greatly increased in number, although it is difficult to decide whether this is absolute or relative. The neuroglia fibers are usually slightly coarser than normal. The tangential fibers of the cortex may be reduced in

number or entirely absent. The ganglion-cells exhibit a great variety of alterations. The protoplasmic processes are varicose, and when sufficiently well impregnated show the absence of the gemmules. The axis-cylinder is usually distinct, due to the degeneration of the myelin-sheath. The body of the cell may be irregular and vacuolated, and there is often extensive chromatolysis. The ventricles of the brain are usually slightly distended, probably the result of simple atrophy, and the choroid plexus is often cystic. Changes are frequently found in the spinal cord. The ganglion-cells in all parts show pronounced degenerative characteristics. This is particularly interesting in view of the fact that the motor symptoms progress so gradually. The posterior roots are often slightly degenerated, and there is systemic degeneration of the posterior columns not unlike that found in the early stages of tabes dorsalis, excepting that ordinarily it is most pronounced in the cervical region. The pia and arachnoid of the cord, particularly those portions covering the posterior columns, are thickened and more or less adherent. The dura is often markedly thickened and may exhibit pachymeningitis.

INJURIES TO THE CENTRAL NERVOUS SYSTEM

Injuries to the central nervous system produce a great variety of lesions, according to their nature and severity.

Concussion, either from a single shock or from repeated blows, may give rise to transient or permanent changes. Ordinarily there is considerable hemorrhage at the site of the blow. This may be either between the dura and the skull or between the arachnoid and the pia. Small hemorrhages are not infrequently found in the central nervous substance, and appear to occur particularly in the direct line of the force applied to the skull. In the latter case autopsies have shown the existence sometimes of multiple hemorrhages, sometimes of disseminated areas of sclerosis in the white and the gray substances. Not infrequently hemorrhage is also found in the subarachnoid space of the opposite side (hemorrhage by *contre coup*). This is explained either by supposing a flattening of the elastic skull or by ascribing it to the force with which the brain rebounds against that side. Occasionally in the spinal cord, after experimental repeated concussions, changes somewhat systemic in character and affecting chiefly the posterior columns have been observed. The hemorrhages may be punctate or, in some cases, particularly if the injury is severe and the arteries are diseased, massive.

Lacerated wounds of the brain are usually produced by fracture of the skull. There is extensive interstitial hemorrhage and softening, and the surrounding tissue is edematous. If only subdural hemorrhage occurs, it may produce compression with secondary yellow softening. Any of these lesions may heal with the formation of a scar and the production of more or less extensive secondary degeneration. Extensive lacerations of the brain are sometimes the result of injury during birth, giving rise to so-called cerebral palsies of childhood. In these cases,

as the central nervous system is not fully developed when the injury occurs, there is hypoplasia of the affected parts.

Punctate wounds of the brain are due to fragments of bone, to sharp instruments, or to bullets. In nearly all cases a certain amount of infection occurs, giving rise to encephalitis. The injured area usually undergoes complete necrosis, and this extends for some distance into the surrounding tissues. The necrotic area is composed of a granular detritus, in the midst of which are found altered blood-pigment and broken-down nuclei. At the periphery there is usually some granulation tissue, proliferation of the neuroglia, and more or less round-cell infiltration, according to the intensity of the inflammatory process. Experimental lesions may be produced in various ways, the most interesting results, perhaps, being those found after the introduction of foreign bodies or after careful aseptic laceration. In either case, shortly after the operation, necrotic changes will be found in the injured area. There is marked proliferation of the neuroglia cells, even as early as the third day, and of the neuroglia fibers. New capillaries may be seen pushing into the area, the endothelial cells of their walls exhibiting karyokinetic figures. The nervous tissue in the immediate neighborhood is in various stages of degeneration. If there has been much hemorrhage, the blood-pigment will be found in irregular homogeneous masses or in the form of hematoidin crystals. Later, evidences of regeneration in the nervous tissue may be observed, particularly the appearance of karyokinetic figures in the nuclei of the ganglion-cells. The injured area is ultimately replaced by a mass of coarse neuroglia fibers containing, usually, fewer cells than normal. That true regeneration of the central nervous system ever occurs in the human body is exceedingly doubtful; indeed, it is not certain that it occurs in any of the vertebrates, although after removal of the tail in lizards a spongy mass of neuroglia may be found in the new organ.

Compression of the brain is due to tumors or to various infiltrative and exudative processes more or less localized. The most common are those occurring from hemorrhage between the skull and dura, or between the latter and the pia. (See Concussion.) The effect is to compress the gyri, causing interference with their function, blood-supply, and nutrition. The foreign mass may be partly absorbed, but usually something remains, like a cyst with thickening of the meninges, pressing into the brain substance, with the formation of concavities of various shapes (traumatic porencephaly).

INFECTIOUS DISEASES

Tuberculosis occurs in the brain in the form of *miliary tubercles* or as large masses, the so-called *solitary tubercle*, or *tyroma*.

The condition is always secondary and comes through the blood-stream or by extension (bone), usually the former.

Miliary tubercles are met with in association with tuberculous meningitis. They are most frequent at the base of the brain.

Solitary tubercles occur independently of tuberculosis of the meninges. They are more frequent in children than in adults, and usually occur in cases in which there is tuberculosis of other parts of the body, notably the lymphatic glands. The infection reaches the brain through the blood-vessels. The lesions are rounded masses of grayish or yellowish color, sometimes showing fresh gray tubercles at the periphery. The growth of the mass is caused by increase in size of the original tubercles with inclusion of new-formed tubercles at the periphery. Early caseation is usual. Secondary infection of the pia sometimes occurs.

Occasionally there is a sclerosis in the vicinity of the large mass, arising from glia proliferation or from fibrous tissue in the adventitia of blood-vessels.

Syphilis appears in the brain in the form of gummata or as a diffuse vascular disease with secondary degenerative conditions.

Gummata usually begin in the subarachnoid space, originating in the membranes and involving the brain substance secondarily. The dura may be simultaneously involved, and the three membranes may be adherent to each other and firmly attached to the brain. Primary gumma of the brain substance is certainly very rare. In the earlier stages the gumma is a grayish and rather translucent growth, but secondary caseation occurs so rapidly that the primary stage is rarely observed. As a rule, the lesion appears in the form of an irregular, dry, caseous area occupying the cortical portion of the brain and attached to the pia and arachnoid, and even the dura. The cerebral substance surrounding the growth is more or less softened and degenerated. The blood-vessels in the affected area or its vicinity are the seat of endarteritis, which in some causes complete occlusion of the lumen. In hereditary syphilis symmetric gummata of the brain are occasionally found.

Syphilitic disease of the blood-vessels of the brain takes the form of more or less diffuse peri- and endarteritis. Secondary degenerations and softening, or sclerosis, of a diffuse or focal character, may result from the vascular disease, but neither these changes nor the vascular changes are peculiar and distinctive.

Actinomycosis of the brain is generally secondary to actinomycosis of the tissues of the neck, and results from extension upward through the base of the skull. The membranes are first involved, the brain substance secondarily. The lesion may take the form of a chronic abscess or may be tumor-like in appearance.

TUMORS

The most common is probably glioma, but almost equally as common is sarcoma. Cholesteatoma, lipoma, endothelioma, and teratoid cysts also occur, but they spring from the membranes and have been described in connection with them.

Glioma usually appears as an infiltrating mass, causing little alteration in the structure of the brain, somewhat harder in consistency

than the brain substance and slightly darker. It is rarely a multiple growth, and shows no marked predilection for any particular portion of the brain, although it occurs more frequently in the cerebral hemispheres than in the basal ganglia or the cerebellum. It always springs from the neuroglial tissue of the central nervous system, and is remarkable for its extreme richness in cells, that by suitable staining methods may be shown to possess protoplasmic processes (*astrocytes*). These protoplasmic processes, either wholly or in part, form the so-called matrix of the tumor, which appears to be composed of numerous fine, interlacing fibers, in the midst of which, by the ordinary staining methods, the cell appears to lie. Usually, the tumor is exceedingly vascular, the vessels consisting of small capillaries or larger spaces lined with endothelium, and this vascularization may be so excessive that the tumor in parts has a delicate pinkish or reddish color, giving to the cross-section a mottled appearance. In some cases the consistency of the tumor is quite hard, and in these the cellular elements are decreased in amount proportionately to the fibrous tissue. Ordinarily true nervous tissue is absent from the midst of the tumor, the mass in the center being made up of the neuroglia tissue. This gradually diminishes toward the periphery, and ultimately fades into the true nervous tissue that may be somewhat edematous. In some cases, however, as in ordinary sclerosis of the central nervous system, myelinated nerve-fibers may be found in the midst of the tumor, and it frequently happens that the secondary degeneration extending from a glioma is much slighter than the apparent extent of the process would lead one to expect. Occasionally, either glioma cells, or possibly ganglion-cells, that have undergone proliferative changes in the midst of the growth, may be found. These are much larger than the ordinary cells, and contain numerous branched processes and often one or several large nuclei. This is the so-called *ganglionar neuroglioma*.

Some pathologists hold that the starting-point of glioma is always one or more ependymal cells that have been displaced in embryonal existence and have failed to assume the type of glia-cells, basing their theory in part upon the atypical shape of many of the glioma-cells. Sometimes the cells of gliomata arrange themselves in rosettes, as if forming the lining of a channel. These have been interpreted as remains of embryonic ependymal structures, and the name *neuro-epithelioma* applied when such formations are numerous; these tumors have been found in specialized nervous tissue like the retina.

Sarcoma of the brain is probably the next most frequent tumor. It usually occurs in middle adult life, although it is quite frequent in children. The commonest seat is the cortex, which it probably invades from a primary focus of proliferation in the membranes. The tumors are ordinarily nodular growths, usually distinctly circumscribed from the surrounding tissue, and in some cases even surrounded by a fibrous capsule, from which they can be readily removed. They are rather firmer than the brain tissue, and sometimes slightly umbilicated if at the surface. The surface of section is pale and dry, but frequently

mottled on account of the presence of hemorrhages. If primary, the sarcomata are single; if secondary, more frequently multiple. Histologically, almost any type of sarcoma may be found, the most frequent perhaps being the round-cell, non-pigmented form. Giant cells are very frequently found. Ordinarily the tumors are extremely vascular, and occasionally contain interstitial hemorrhages. The surrounding brain tissue shows the symptoms of marked compression, is edematous, and may contain small interstitial hemorrhages. The true nervous substance is ordinarily degenerated, and we find extensive secondary degeneration as a result of the presence of the tumor.

Many authors believe that a combination of glioma and sarcoma may occur, and gliosarcomata have been frequently described. As the neuroglia tissue has the functions of connective tissue, and in many

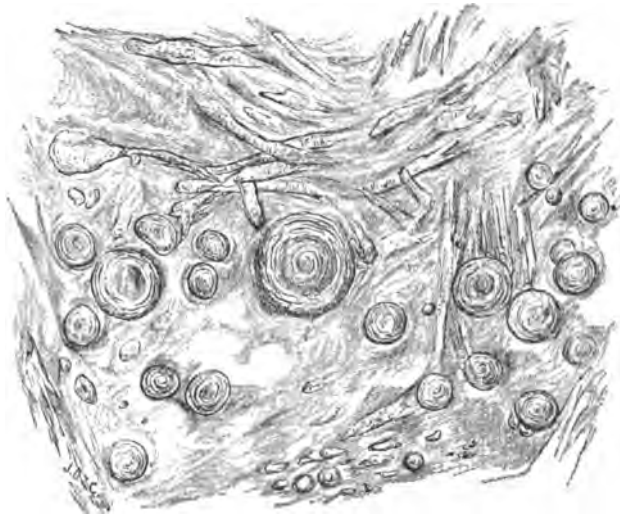


Fig. 428.—Psammoma, showing calcareous spicules and whorls.

respects resembles it in its pathological processes, it is natural that a glioma should be similar to a sarcoma, and this has possibly caused an error of diagnosis in some cases. As the two tumors arise from tissue of different natures and develop in different situations their combination is theoretically unlikely.

Certain forms of tumors have been described that appear to spring from the adventitia of the blood-vessels. They consist of masses of cells usually sharply circumscribed, somewhat cylindrical in shape, having in their center a small lumen in which blood-cells may sometimes be detected. These are the so-called *perithelioma* or *angiosarcoma*. Such tumors in all probability come from the meninges in most cases.

Fibroma occurs as a hard, circumscribed tumor, sometimes found in the hemispheres, but it is extremely rare.

Lymphangioma appears to arise from the pia.

Osteoma is usually an extension inward from the skull or membranes, but occasionally occurs as a tumor, apparently originating in the brain substance, forming hard masses from the size of a pea to that of a cherry, and somewhat irregular in shape.

Psammoma.—This special term has been given to tumors containing calcareous granules. It has been mentioned in connection with the choroid plexus and the membranes. Occasionally circumscribed fibrous tumors containing calcareous granules are found in the brain substance, but these are extremely rare (Fig. 428).

Carcinoma of the substance of the brain is invariably a metastatic growth. It appears either as small, round, circumscribed nodules, of firm consistency and pale color; or as larger, more or less infiltrating masses with softened interior. It usually replaces entirely the nervous tissue, either pushing it aside or destroying it, and gives rise, therefore, to more or less pronounced secondary degeneration. Multiple metastatic carcinomatous growths, however, may exist in the brain without causing clinical symptoms.

THE CHOROID PLEXUS

The **choroid plexus** consists of a plexus of vessels derived from the mesoblast, that are everywhere covered by a layer of cuboidal or columnar epithelium. Histologically, it consists of an inner layer of endothelial cells and an outer layer of epithelial cells, separated by a small amount of areolar fibrous tissue. The structure of the choroid plexus, therefore, bears a very close resemblance to the structure of the glomeruli of the kidneys, and, as it is obvious that the blood-vessels of which it is composed can have no nutritive function, excepting in so far as they supply the epithelium that covers them, it has been supposed that the choroid plexus is a secretory organ, its object being to secrete the cerebrospinal fluid. This theory is sustained by the facts that the cerebrospinal fluid differs in composition from the lymph, or from the fluid poured out in serous exudations, and that extracts of the choroid plexus will stimulate the secretion of the fluid in experimental animals. The choroid plexus probably also acts as a barrier to the entrance of toxic substances to the spinal fluid.

Hypersecretion.—In certain cases in which communication between the cavities of the brain and the exterior exists—as, for example, through the ethmoid plate of the nose—there is distinct hypersecretion of the cerebrospinal fluid. In a case described by St. Clair Thomson as much as a pint was discharged in twenty-four hours. In these cases, if for any reason the flow is checked, symptoms of intracranial pressure occur. Regarding the pathological changes in the choroid plexus that are associated with this condition we have at present no information. Hypersecretion probably also takes place in all inflammatory conditions.

Inflammation.—In inflammatory conditions, particularly meningitis, encephalomyelitis, either separate or combined, and associated with the presence of an abnormal quantity of albumin in the cerebrospinal fluid, more or less inflammation of the choroid plexus is usually found. This

is indicated particularly by round-cell infiltration about the vessels and beneath the epithelium. Sometimes there is a slight amount of exudation upon the epithelial surface, and occasionally small foci of suppuration can be detected.

Infectious Diseases.—Among the infectious diseases the only one of importance is tuberculosis. In this condition miliary tubercles or large cheesy foci may be found.

Chronic inflammation appears to be exceedingly rare, or, what is probably more accurate, has rarely been described, for there is every reason to believe that the choroid plexus shares in all conditions that involve the pia mater. Atheromatous conditions seem to be very infrequent, but a certain amount of thickening of the walls of the vessels may be observed in old age. A certain amount of overgrowth of connective tissue, sometimes associated with slight round-cell infiltration, is also occasionally found in old people.

Hemorrhage may take place into the choroid plexus, and is usually an agonal phenomenon.

Degenerations.—*Calcification* is the most frequent of the infiltrations. This may be recognized by the gritty sensation upon cutting into the choroid plexus. Microscopically, the calcareous nodules appear as minute dark granules that stain purplish with hematoxylin. Masses of cholesterin are by no means uncommon; they rarely present the form of typical cholesterin plates, but are somewhat irregular in outline, of a faint yellowish color, and shine brightly when examined by oblique light. Both conditions are common in old people.

Pigmentary infiltration probably also occurs, certainly in malaria, and perhaps in old age.

Ependymitis of ventricles may be chronic or acute. The acute form is always secondary to meningitis, and is characterized by proliferation of the ependymal cells and the usual inflammatory changes. Chronic ependymitis is usually associated with sclerosis of the brain. The surface is granular or even nodular. The ependyma is thrown into folds, and there is great proliferation of the subependymal neuroglial fibers (Fig. 429).

Tumors.—A great variety of tumors occurs in the plexus. *Cysts* may be either retention or extravasation cysts, or parasitic. The retention cysts may be lined with epithelium, and probably represent adhesions at the edges of fissures with persistence of secretory activity. More commonly they are lined with endothelium and represent dilated lymph-spaces. They may be single or multiple, and appear as small translucent sacs, filled with a clear, slightly yellowish liquid, or else a colloid-like, viscid mass. Parasitic cysts are usually due to *Tania solium*. They may be either single, the *Cysticercus cellulosæ*, which may be attached to the plexus or lie free in the ventricular cavity, or multiple, forming the so-called *Cysticercus racemosa* of the brain.

Among the benign tumors, *fibromata*, possibly only organized thrombi, and *lipomata* have been described. A *dermoid cyst* has been reported by Lebert. *Endotheliomata* may spring from the lymphatic spaces. *Epi-*

theliomata, or *ependymoma*, may arise from the epithelial covering. Two varieties have been described: the *papillomatous* and *cylindrical cell tumor*. These tumors are rarely uniform in character or pure in cell content; they are apt to show solid and cystic areas, and to contain some nervous tissue elements. They are usually single growths and do not give metastases.

The **cerebrospinal, or arachnoid, fluid** is a clear, limpid, colorless or slightly yellow liquid occupying the meshes of the arachnoid, the subdural space, and the free cavities of the central nervous system. It is said to vary in amount from 50 to 100 c.c., but only a small portion is obtained by spinal puncture. It is faintly alkaline in reaction and salty in taste; its specific gravity is about 1008, varying slightly in health and but little in disease, except when the liquid is distinctly purulent, it then being notably heavier. The fluid is produced by filtration through the choroid plexus by filtration and by the secretory

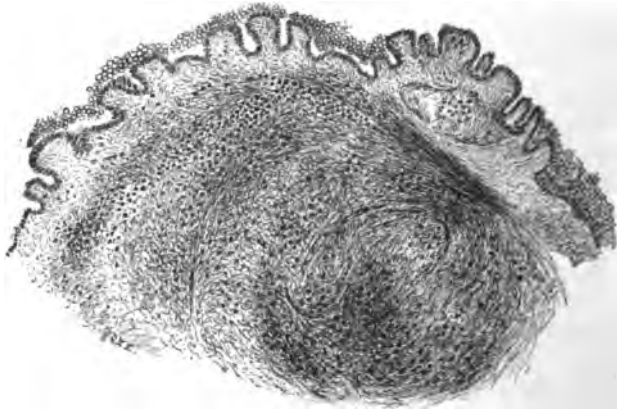


Fig. 429.—Sclerotic nodule in the floor of the lateral ventricle, with wrinkling of the ependyma; $\times 100$ (Sailer).

power of this organ, by the perivascular tissue of the nervous system, and possibly by the arachnoid villi. It returns to the circulation via the last, and by way of the veins and lymphatics. Its accumulation in disease is due to overaction of the sources by congestion and to obstruction to its escape by inflammatory lesions of the meninges. In health the fluid contains a small quantity of globulin, nucleoprotein, albumose, and urea; a reducing body is also usually present. Under pathological conditions any or all of these may be increased. The cells of the fluid are only mononuclear, lymphocytic and endothelial, during health, and are about 10 per cubic centimeter. The fluid, as determined by measurement in the spinal column, has a pressure of about 120 to 160 mm. The functions of the cerebrospinal fluid are to act as a mechanical support and protection to the central nervous system, and it may be a medium of metabolic activity for the superficial parts of the brain.

In disease so many modifications are possible that only the most characteristic can be given for the various important conditions. So far as quantity is concerned, the only change seems to be in the direction of increase. This is brought about by inflammatory lesions, decrease of blood-pressure, or to venous obstruction. Within the ventricles increase of the fluid and its pressure are caused by an obstruction to the passage of fluid from the ventricles and aqueduct of Sylvius through the foramen of Magendie.

Cerebrospinal meningitis of the epidemic form shows in early stages a cloudy fluid, but soon a distinctly purulent character is assumed. Cells up to many thousands per cubic centimeter are found. Micro-organisms are found within the cells and free in the fluid. Protein contents are naturally much increased. The pressure may rise to 250 mm. Meningitis of pneumococcus origin will give similar conditions, while in influenzal cases the fluid is not rarely hemorrhagic, or at least blood tinged.

Tuberculous meningitis gives, as a rule, an excessive, clear fluid in which a delicate coagulum will form on standing; occasionally the fluid is turbid. The pressure is increased to a variable extent. Protein is increased as is the cellular content; mononuclears usually predominate, but polynuclears may be numerous.

Paresis and Tabes.—In these conditions the amount of the cerebrospinal fluid is usually increased, but not always, and the significant features are a pronounced increase in mononuclears and an excess of globulin. The fluid may also contain the antigen of syphilis and may be used in the Wassermann test.

Poliomyelitis.—In the very early stages the fluid may be slightly turbid, but it shortly becomes clear; occasionally spontaneous coagulation with a very faintly cloudy clot is seen. The protein, globulin, is increased early in the disease and usually remains in excess throughout the attack. No great excess of cells is found; polynuclears may be as numerous as mononuclears. The fluid in poliomyelitis is in great excess, and may be as high in pressure as in pyogenic inflammatory diseases. It rarely contains the virus.

Trypanosomiasis gives an excess of clear or slightly turbid spinal fluid in which an increase of mononuclears and of the globulin may be found; the trypanosomes may also be present.

The *Spirochæta pallida* has been found in the fluid in cases of active nervous system syphilis.

Hydrocephalus.—Excess in quantity of the cerebrospinal fluid in the ventricles is known as hydrocephalus. This may be produced by a great variety of causes. It may be congenital and perhaps due to a malformation, but is more often a result of disease. Congenital hydrocephalus frequently appears to be due to some defect on the part of the parent, and is particularly common in the children of drunkards.

Congenital hydrocephalus internus is characterized by a gradual accumulation of cerebrospinal fluid in the lateral and third ventricles of the brain, probably the result of excessive secretion from the choroid

plexus, with some anomalous formation to prevent its escape or absorption (Fig. 430). As a general rule, the fourth ventricle is not involved. The aqueduct of Sylvius, however, is often dilated. Sometimes the fifth ventricle is distended or the septum has atrophied and disappeared, allowing free communication between the two lateral ventricles. Less frequently the infundibulum is distended and forms a small sac at the base of the brain. Usually the disease is manifest at the time of birth, and the head may even at this period have attained the circumference of more than 50 cm. Externally, the head is spherical and large; the face is small, and, with the bulging forehead, gives to these patients a characteristic expression. The cranial bones are usually more or less



Fig. 430.—Congenital internal hydrocephalus, with marked atrophy of the white substance (from Bollinger).

separated; frequently the edges of the sutures are an inch or more apart. The anterior fontanel is large and usually bulging. If the bones of such a skull be examined, it will usually be found that they are very thin and that ossification is incomplete. The dura mater is tense, and beneath it may be found the greatly flattened convolutions. The brain substance seems softer; often there is distinct fluctuation, although the brain collapses as soon as it is removed from the cranial cavity. The distance from the wall of the ventricle to the surface is much less than normal, this atrophy seeming to affect the white substance more than the cortex. The total weight of the brain, however, is often normal or nearly so, and it is impossible to say that an actual atrophy has really taken place. The substance of the brain is pale, probably as a result of the pressure, and often softened, particularly in the neighborhood of the ventricles, although this is probably only an unusually rapid postmortem change. The floor of the ventricles may be smooth or slightly

roughened, and occasionally distinct nodules may be observed. In the latter case there is usually considerable proliferation of the neuroglia in the cortex, and just beneath the floor of the ventricle a sort of sclerosis of the brain substance. The cerebrospinal fluid is usually clear and not abnormal in consistency. Occasionally, however, it is somewhat turbid, particularly if there are any signs of old inflammatory action. The choroid plexus is often somewhat enlarged, pale, and may contain cysts. As the patients increase in age there is usually considerable increase in size of the head; nevertheless, the convolutions gradually become more rounded and the white substance appears to undergo a sort of redevelopment, for the layer of brain tissue between the ventricle and the surface

becomes thicker. Systemic degenerations of the white fibers are uncommon. There may, however, be marked thinning of the corpus callosum and the anterior commissure. Cases have been described in which a descending degeneration along the pyramidal columns was found in the cord.

Partial hydrocephalus has been described. It is probably, in the great majority of cases, of congenital origin. It may affect only one ventricle, or even only a part of a ventricle, as, for example, the anterior or posterior horn of one of the lateral ventricles. It appears to be the result of an obliteration of one of the normal passages by which the ventricles communicate with one another.

External hydrocephalus is the accumulation of fluid that occurs in the subarachnoid space to replace brain tissue that has undergone atrophy, or to fill the cavities in porencephaly. Occasionally symmetrical collections of liquid are found, as in a brain removed from an idiot, in which both temporosphenoidal lobes were excavated and replaced by large cysts.

Acquired hydrocephalus may be either acute or chronic. The acute forms are usually secondary to inflammatory changes in the meninges, extending to the choroid plexus and to the ependyma, or are caused by some abnormal growth pressing upon the veins of Galen, or to obstruction of the aqueduct of Sylvius or the foramen of Magendii. In the atrophic brains of the aged dilated ventricles are frequently found.

Acute acquired internal hydrocephalus is usually the result of acute basilar meningitis, either inflammatory or tuberculous. The brain, in addition to the changes in the meninges, presents all the characteristics of intense intracranial pressure. The convolutions are flattened and pale. The brain tissue is usually soft, or at least softens rapidly after death, particularly the part that surrounds the distended ventricles. Upon opening the brain the fluid is usually found under considerable pressure, and often almost gelatinous in consistency. Frequently, microscopical examination of the brain substance will show the presence of acute, disseminated, suppurative encephalitis. The ependyma of the ventricles is injected and often covered with lymph. In the tuberculous form it may be roughened, as a result of the presence of numerous miliary tubercles. The choroid plexus is injected; in the acute forms it also has some lymph upon the surface, and in the tuberculous form may contain miliary tubercles.

Chronic hydrocephalus is usually a late result of meningitis, particularly the epidemic form. Occasionally it is the result of gradual compression of the veins of Galen, or obstruction to the course of the liquid from the lateral ventricles to the subdural space, as, for example, by a tumor of the cerebellum. Perhaps most frequently it is the result of a chronic granular ependymitis. In these cases the distention is more pronounced than in the acute form. The ependyma is thickened and opaque, and often contains small hard nodules. Occasionally, bands of organized fibers may be found in the cavity of the ventricle.

CHAPTER XIII

DISEASES OF THE SPINAL CORD AND ITS MEMBRANES

THE DURA MATER

Diseases External to the Dura Mater.—Among the minor processes that may occur externally to the spinal dura mater is **fatty infiltration**, sometimes associated with general obesity, but occasionally found in patients that are moderately emaciated.

Hemorrhage may occur on the external surface of the dura, the blood being found distributed in the extradural areolar tissue. The usual cause is traumatism, but it may also occur in convulsive conditions. Ordinarily, the blood remains circumscribed and forms a spinal hematoma; rarely, a cyst results.

Diseases of the Dura Itself.—Most of the pathological processes are secondary to some disease of the vertebral column. The most important is tuberculosis; this gives rise to **external tuberculous pachymeningitis**, characterized by a collection of cheesy material which may have undergone either softening or necrosis, or else contains pus-cells. The dura in the affected region is usually considerably thickened, and may have upon its inner surface a slight amount of exudate. The char-



Fig. 431.—Tuberculous pachymeningitis secondary to spinal caries.

acter of the lesions is not different from that of tuberculosis in other serous membranes (Fig. 431).

Pachymeningitis cervicalis is a localized tuberculosis or syphilis of the dura mater occurring in the cervical region, and characterized by considerable thickening, sometimes amounting to $\frac{1}{2}$ cm. or more. The dura is usually adherent to the spinal canal and to the arachnoid and pia, the latter showing more or less involvement. The serious changes consist of compression of the roots and of the spinal cord, the latter especially in the anteroposterior direction. The process may extend into the substance of the cord and produce a myelitis of the periphery, and occasionally extends deeper and causes more or less extensive secondary degenerations.

Of the acute inflammations the most important is **internal hemorrhagic pachymeningitis**, a process similar to that occurring in the dura mater of the brain. It consists of a layer of granulation tissue in which many of the capillaries have ruptured, giving it a more or less uniform reddish appearance; it is somewhat irregular in outline and of varied extent, and not infrequently adhesions form between the dura and the arachnoid.

Syphilis occurs either in the form of discrete gummata or as a regular and diffuse thickening of the inner layer.

Tumors of the dura are rare, but when present grow inward, compressing the cord and giving symptoms of transverse localized disease. Tumors from the spinal canal frequently invade the dura.

Lipoma is the commonest benign tumor. *Myxomata* and *fibromata* are exceedingly rare. *Chondroma* has been observed.

Sarcoma may be of the round-cell, angiomatous, or alveolar type. It is usually irregular in outline, spreading like a fungous mass over the surface of the membrane, which exhibits fibrous thickening. If small and occurring on the anterior aspect, it may produce no symptoms whatever. In this situation it is frequently secondary. In a few rare instances melanotic sarcoma has been observed. Not infrequently a granular sarcomatous mass invades the cauda equina and infiltrates it for a considerable distance downward. The nerve-roots often fail to show any signs of degeneration, and apparently no pressure symptoms are produced. In some cases sarcomata of the dura produce proliferation of the neuroglia tissue in the adjacent portion of the spinal cord.

Upon the inner surface a variety of tumors have been observed. Horsley mentions myxomata, fibromata, carcinomata, and sarcomata. In rare cases echinococcus cysts have been observed, and even the cysticercus.

THE PIA-ARACHNOID

CIRCULATORY DISTURBANCES

Active hyperemia precedes and accompanies inflammatory changes. It is rarely seen postmortem, and in the majority of cases its existence can only be inferred.

Passive hyperemia is very common—that is to say, in many cases the veins of the pia mater are found to be tortuous and greatly distended with blood. This is usually due to postmortem hypostasis.

Hemorrhage may occur from traumatism or the rupture of small aneurysms, the most frequent place for the latter being the cervical or basilar region.

DEGENERATIONS

Calcareous infiltration sometimes occurs, appearing as small, hard plates, rarely more than 0.5 cm. in diameter, scattered along the whole length of the spinal cord. It is probably always secondary to inflammatory processes, as spinal syphilis and tuberculosis.

INFLAMMATIONS

Acute inflammation, or **acute leptomeningitis**, is often secondary to cerebral meningitis. It may occur, however, independently as a result of local suppurative processes, particularly those of the spinal column. It may be serous or purulent in character, and in the latter an exudate is found upon the inner surface of the dura and in the sub-arachnoid space, often extending the entire length of the spinal cord. The microscopical changes are essentially similar to those found in the membranes of the brain. Involvement of the cord is, however, much more common. There is usually extensive round-cell infiltration in the anterior commissure and small foci of round cells scattered throughout the gray and the white matter, especially in the latter. Frequently these can be seen to surround a blood-vessel, but this is not always the case, and it is not unlikely that purulent material can enter from the lymphatics of the pia. The covering and interstices of the nerve-roots are commonly infiltrated. If death does not occur, adhesions may form between the dura and arachnoid, but these are certainly exceedingly uncommon in the cord.

Chronic leptomeningitis is usually associated with sclerosis of the spinal cord; thus, in locomotor ataxia the pia mater over the posterior column may be opaque and slightly thickened. It may also be consecutive to some of the other inflammatory processes, and in this form adhesions may be found between the dura and arachnoid (*pachymeningitis* and *arachnitis adhesiva*).

In cases of injury of the spinal column, such as fracture, caries, etc., in which continuous pressure is produced upon the dura mater, it becomes thickened and adherent to the bone and to the pia and may cause pressure upon the spinal cord. In these cases there is rarely any round-cell infiltration in the thickened dura, which consists almost entirely of fibrous connective tissue and blood-vessels; the latter have greatly thickened walls.

INFECTIOUS DISEASES

Tuberculosis may occur in the form of miliary nodules or as small cheesy masses, usually extending a slight distance from the pia mater into the substance of the cord. It is disputed whether an acute leptomeningitis without miliary or cheesy nodules may be caused by this organism alone, but, while it is probable that such inflammation may occur, this has not as yet been definitely established. Solitary tubercles may occur in any part of the spinal cord. They are rarely encapsulated. Tuberculous meningitis is hematogenic, or arises by extension. The localized form is commonly the result of Pott's disease. A generalized form occurs in connection with cerebral meningitis (*q. v.*).

Syphilis appears as a thickening of the membranes with multiple gummata, often projecting into the substance of the cord or extending to and involving the dura mater. The vascular changes are very char-

acteristic; nearly all the blood-vessels exhibit the typical round-cell infiltration and thickening of the intima which have been described in the section on endarteritis syphilitica. There are also a perivascular round-cell infiltration and some proliferation of the adventitia. The veins may also be involved. The lumen of both sets of vessels is usually contracted, and there is a great tendency to the formation of thrombi. In these thrombi organization may take place, with the formation of new blood-vessels. The spinal cord may also exhibit various lesions, due either to pressure or to direct extension inward from the pia.

In congenital syphilis the upper part of the spinal cord appears to be more involved than the lower part. In syphilitic leptomeningitis there are often extensive degenerations of the tracts in the cord. These involve particularly the lateral and posterior columns, giving rise to a combined sclerosis; and, in addition, there is often a narrow band of sclerotic tissue encircling the cord and lying immediately beneath the pia.

Tumors of the pia are principally angiomas, endotheliomas, and fibromas; sarcoma and degenerative tumors like myxoma may occur. Neurofibroma, chiefly near the nerve-roots, is reported. Secondary tumors are carcinoma, sarcoma, and so-called myeloma. They produce symptoms like those noted under the dural tumors.

ANATOMY OF THE CORD

The spinal cord is composed, as are the other parts of the central nervous system, of gray and white matter, the gray matter occupying the central part and the white matter being distributed around it. The cord is of varying size, somewhat broader and flatter in the cervical region than elsewhere; almost circular in the dorsal region, and again thicker in the lumbar region. It communicates with the rest of the body by means of the spinal nerves, which arise anteriorly and posteriorly as roots. It is surrounded by three membranes: the pia, adherent to it; the arachnoid, adherent to the pia, but not dipping into the anterior fissure, and the dura mater, which is adherent neither to the arachnoid nor to the vertebral column. The gray matter is divided into two parts by the anterior commissure and posterior septum, each part consisting of an anterior horn, a thick, roundish mass, and a posterior horn, a slenderer projection. The lateral halves are united by the gray commissure, in which is the central canal lined with cuboidal epithelium and continuous with the fourth ventricle above. In the anterior cornua are found the large multipolar ganglion-cells, whose axis-cylinders pass out through the anterior roots and end in the muscles; commencing in the dorsal region, there is a group of cells in the inner portion of the posterior horn, near the gray commissure, which are bipolar and whose axis-cylinders pass outward to the cerebellar tract, in which they ascend to the vermiform process of the cerebellum. The posterior roots are composed of fibers that originate in the spinal ganglia and pass into the cord. These spinal ganglion-cells have a single process, which appears to divide into two fibers, one passing outward into the peripheral nerves and usually terminating in the sensory corpuscles of the skin, the other passing inward through the posterior root to the spinal cord. The white substance of the spinal cord is composed of bundles of nerve-fibers that have, for the most part, a common function, a common mode of origin and of termination.

Anatomically, the cord may be divided into three regions: anterior, lateral, and posterior, although these do not correspond to regions embryologically distinct. According to the manner of development, it should be separated into the anterolateral and the posterior regions.

The most important bundles of fibers in the anterolateral columns are those known as the *pyramidal tracts*, for the reason that they are continuations of the pyramids of the medulla. They originate in the motor region of the cerebral cortex and, in the first cervical segment, decussate through the representatives of the anterior cornua to reach their situation in the lateral columns. This decussation does not occur in all of the fibers, many passing down in the direct pyramidal columns and some without decussation in the lateral columns. These undecussated fibers subsequently cross to the other side through the anterior or white commissure. The fibers of the pyramidal columns terminate in arborizations which surround, but are not in contact with, the ganglion-cells of the anterior cornua.

The cerebellar tract has already been described. Anterior to it and close to the periphery of the cord is the so-called *anterolateral column of Gowers*. The fibers which form this probably originate in the lateral groups of cells in the anterior cornua and in the cells in the middle portion of the spinal cord. The column increases in size upward and degenerates in the same direction. Its termination is unknown. It also contains fibers that degenerate downward, of whose origin and termination we are ignorant.

The rest of the anterolateral column is composed of short fibers, uniting different segments of the spinal cord.

The posterior columns are composed of the fibers that enter by the posterior roots. These fibers divide into two branches, one ascending and the other descending, the latter terminating in the gray matter of the posterior horn. The ascending fibers may be divided into two groups, the lateral and median bundles. The fibers of the lateral bundle are somewhat finer and evidently belong embryologically to a different period, because they acquire their myelin-sheaths later. They pass directly into the zone of Lissauer, and thence into the substantia gelatinosa of Rolando, and some of them terminate in arborizations about the ganglion-cells in the column of Clarke. The fibers of the median bundle are coarser. They pass inward, then upward along the inner side of the posterior horns, and then become the *column of Burdach*. The median fibers from the lower part of the cord bend inward and continue their course in the column of Goll, terminating finally in the nucleus gracilis of the medulla oblongata. The fibers that enter the cord in the cervical region pass upward in Burdach's column and terminate in the nucleus cuneatus. Other fibers pass forward to the ganglion-cells of the anterior cornua, and have been supposed to be concerned in reflex action. Others decussate in the posterior commissure and then pass upward in the posterior columns of the opposite side. At somewhat regular intervals they give off at right angles fine collateral branches, which pass forward, and some of them, at any rate, end in arborizations about the cells of the anterior cornua of the gray matter. These are known as the reflex collaterals of Kölliker. A small portion of the posterior column just back of the gray commissure appears to be composed of fibers uniting the different segments. Physiologically, the spinal cord may be regarded as a series of superimposed centers which contain cells sending or receiving impulses to or from the periphery, and bands of fibers that unite these centers with the brain. The functions of these different tracts have already been discussed in the Anatomy of the Brain. An important function of the spinal cord is the accomplishment of reflexes. The centers for these reactions are situated in various portions, and according as these portions are intact or involved the reflexes persist or disappear. By means of the distribution of the sensory and motor disturbances and the alterations in the reflexes, accurate localization of a lesion in the cord is often possible.

The lymph-channels of the cord are of some importance in inflammations by continuity. The conclusions of Bruce and Dawson upon their anatomy indicate that they follow the adventitia of the capillaries, veins, and arterioles toward the surface of the cord where they enter the deep layer of the pia, through which they probably communicate with the subarachnoid space. "The lymphatic path has in the main an outward direction, but there is no doubt that it permits of a current inward, or of an invasion by cellular elements, micro-organisms, and toxic substances."

CONGENITAL ABNORMALITIES

Total absence of the cord, or amyelia, only exists in association with anencephalus. It is interesting to note that the spinal ganglia usually persist.

Abnormal smallness is known as **micromyelia**. The cord may be normal in structure, all the elements being proportionately reduced, but more commonly only certain parts are affected, particularly the pyramidal columns, as a result of fetal lesions in the motor tract.

Double cord, or diastematomyelia, is usually localized to one portion of the cord, particularly the lumbar region. Occasionally the cord is completely divided by a bony septum. In this case the gray matter in either half presents the normal arrangement of the gray matter in the cord.

Unusual length of the cord may also occur, the *conus terminalis* being in these cases elongated and extending to the end of the sacrum. The spinal roots may be excessive or defective in number on one or both sides. This usually occurs in the dorsal region, the commonest condition being the presence of eleven roots on one side. The cord may be asymmetrical. This usually involves only the pyramidal columns, and is due to incomplete decussation.

Heterotopia of the gray matter is not infrequent. This may consist of doubling of one of the horns, abnormal relation of gray and white matter, disorganization of one or both horns, or fissures extending into the substance. According to van Giessen, the majority, if not all, of these cases are the result of injury during removal, and are therefore to be regarded as artefacts. This statement is, however, too sweeping. Abnormal bundles, producing heterotopix and due to alterations in the medulla or even higher in the central nervous system, have been found. These appearances may also be produced by tumors or other conditions causing pressure.

Dilatation of the Central Canal.—The central canal may be dilated, either locally or throughout its whole length. This condition is known as *hydromyelia*, or *hydrorrhachis*, and is akin to hydrocephalus, with which it is sometimes associated. Hemorrhage may take place into these dilated canals and gives rise to *hematomyelia* (*vide infra*).

Localized collections of liquid in the subarachnoid spaces are sometimes spoken of as *hydrorrhachis externa*.

Spina Bifida.—There may be imperfect closure of the posterior processes of the vertebræ, giving rise to clefts, which are known as *rachischisis*. If the membranes of the spinal cord protrude through the cleft in an imperfectly closed canal in the form of a sac or hernia, the condition is called *spina bifida*. In some cases the skin is still present, and is often covered by an abnormally thick growth of hair. In other cases the pia is the only membrane that enters into the formation of the wall. It is usually thickened, and may be covered with granulations. The spinal cord may be incompletely or normally formed and hang in the sac. Sometimes the dilatation evidently takes place

in the central canal, for the substance of the spinal cord may be recognized adhering to the inner layer of the pia mater. This condition is called *myelomeningocele*. *Spinæ bifidæ* usually appear in the sacral or lower lumbar region, although *rachischisis* may involve the entire length of the vertebral canal.

Rarely a cystic dilatation of the meninges may take place between completely formed vertebral arches.

HYDROMYELIA AND SYRINGOMYELIA

Hydromyelia is a condition in which the central canal of the spinal cord is dilated. It frequently occurs in circumscribed portions and is apparently without clinical significance. More rarely the whole canal has a macroscopical lumen throughout its entire length, particularly in cases of hydrocephalus, although in the majority of cases of this latter disease the spinal cord is not involved. A patulous canal can be distinguished from a pathological cavity by the fact that the canal is lined by the normal cuboidal epithelium of the ependyma. Usually there is a considerable collection of ependymal cells in the neighborhood of the central canal, and this is more apt to be the case if it is dilated or otherwise altered than if it is normal. Occasionally

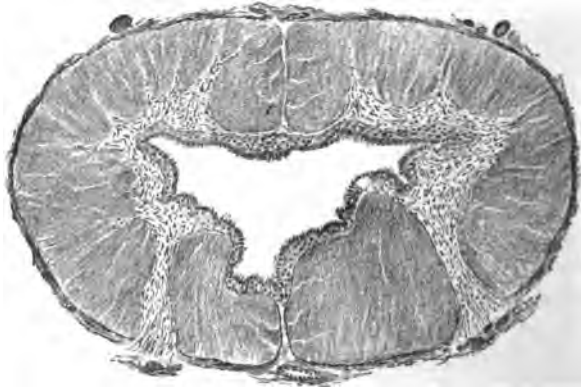


Fig. 432.—Hydromyelia (partly diagrammatic).

the central canal is doubled. This rarely happens throughout the whole length of the cord, but is more frequently found in a limited portion, especially the lumbar region. This doubling is due in some instances to the obliteration of the central part of a dilated canal with its long axis transversely placed. Sometimes a slit-like canal shows a dilatation in only one part. At places the lumen of the canal may be completely obliterated, leaving nothing but a mass of cells in the gray commissure, in the midst of which capillaries may be observed. More distinct pathological changes are diverticula that occasionally spring from the canal. These seem to be most frequent in the cervical and

dorsal regions. They usually extend downward, and are situated posteriorly to the gray commissure. It is possible that collections of epithelial cells from the ependyma under similar circumstances may form masses in the posterior column without distinct cavity formation, although this is doubtful. These changes are particularly significant on account of their relation to the disease known as syringomyelia (Fig. 432).

Syringomyelia.—Pathologically, this is essentially a cavity in the spinal cord that is not lined throughout with the columnar epithelium of the ependyma. This cavity may appear as a wide dilatation or as a narrow slit. It usually occupies the posterior part of the cord, is exceedingly asymmetrical, sometimes limited entirely to one side, and in these cases is ordinarily found in the posterior horn or on its inner side. The cord may be unaltered externally. The dura mater is commonly normal. The pia and arachnoid are either normal or else thickened slightly, the change being not unlike that found in senility or in cases of chronic edema of the membranes. The shape of the cord may be entirely normal. This, however, is rare. Usually there is some asymmetry, and frequently, particularly if the cavity be large, the cord upon being removed and laid upon a flat surface seems to collapse, giving rise to the so-called ribbon appearance. Section through the cord shows the existence of a larger or smaller cavity filled with the products of liquefaction-necrosis, cerebrospinal fluid, or more rarely with blood. Sometimes it appears to have been empty, in which case the cord probably was collapsed in the spinal canal and the space thus formed was filled with cerebrospinal fluid. The solid portion of the cord is usually somewhat darker in color, and the distortion of the outline corresponds to the extent of the process. The portions of spinal cord not involved by the lesion, and below it, commonly show more or less descending degeneration. In the portion above the cavity, if it does not extend as far as the medulla, some degeneration in the posterior columns is often found. In many cases, however, both the ascending and descending tracts are intact; at least they appear so to the naked eye. Microscopical examination shows that the cavity is bounded, as a rule, by a delicate reticulum of hyperplastic neuroglia. Sometimes this is lined with what appears to be connective tissue, and is supposed to be an inclusion of the pia mater; at other times it is lined with ependymal epithelium. The tissue in the neighborhood is usually hyperplastic neuroglia. The cord in the immediate neighborhood may show curiously few changes, the ganglion-cells being perfectly normal and the fibers uninjured. If the cavity is extensive and the proliferation of the neuroglia considerable, this is not the case. An entire posterior root may be destroyed, or perhaps half or more of the spinal cord will be extensively degenerated; in these cases secondary degeneration always occurs. Not only the pyramidal tracts, but also bundles in the posterior columns degenerate downward. In a case that was studied by one of us the comma tract of Schultze was beautifully outlined. The nerve-roots are also usually involved, and there is descending degeneration along the

anterior roots, which may be detected also in the nerves. The posterior roots may show some degeneration, but this is rare and the cells of the spinal ganglia are usually intact. Sometimes there is considerable vascular proliferation in these portions of the cords not unlike cavernous change. There is at times so active a gliosis that a suspicion of gliomatous or sarcomatous change has arisen; the seat of this change is characteristically in the tissue in the vicinity of the central canal.

As syringomyelia is particularly a disease of the central portion of the spinal cord, the fibers that convey pain and temperature sense are essentially involved, and, as a result, one of the characteristic changes is the dissociation of sensation—that is to say, persistence of tactile sensation with thermo-anesthesia and analgesia. In addition, as the cells of the anterior cornua are involved, there is degeneration in the muscles that they supply.

The most widely accepted theory for the origin of this condition is that the process is one of gliosis arising from the ependyma of the central canal, since glia tissue is in all probability the descendent of ependyma. This proliferation of the ependyma and metaplasia to glia tissue is assisted by congenital malformation and vascular conditions of congenital or inflammatory nature. The softening proceeds within the areas of glia proliferation by pressure and lowered nutrition. Conditions favoring hydromyelia will, therefore, predispose to syringomyelia.

CIRCULATORY DISTURBANCES

Diseases of the walls of the blood-vessels are similar to those occurring in the blood-vessels of the other parts of the body. Extensive atheromatous changes are relatively rare. Perhaps the most frequent disease is *hyaline degeneration*, which is exceedingly common in cases of sclerosis, and may occur in early life, even in childhood. It is almost invariably present in the cords of persons dying after middle life. Round-cell infiltration of the intima (*endarteritis*) occurs in syphilis, and also, though less frequently, in tuberculosis. Fibrous thickening of the intima and proliferation of the connective tissue of the adventitia are common senile changes.

Attention has been directed more particularly to these changes on account of the suggestion by Redlich that they are the anatomical basis of paralysis agitans. According to him, the characteristic changes are endarteritis and periarteritis, with extension of the latter process into the surrounding nerve substance and the formation of perivascular insular scleroses. In addition, there is often some degeneration in the posterior columns, and occasionally in the lateral columns in the cervical and lumbar enlargements. The vascular changes, curiously enough, appear to be more severe in the posterior horns than in the other parts of the cord, and amyloid bodies are nearly always present in these regions. However, in examining the cord of a typical case of paralysis agitans one of us failed to find these lesions, while in another case, equally characteristic clinically, they were quite pronounced. More information is to be desired upon this disease.

Miliary aneurysms are very infrequent in the spinal cord. Aneurysms of the vertebral arteries, however, sometimes involving the commencement of the spinal branches, have been reported, but are rare.

Active hyperemia of the spinal cord is rather a clinical hypothesis than a pathological entity. Occasionally, however, the gray matter seems to be slightly darker than normal, and there is rather free bleeding from the vessels cut transversely. In many cases of myelitis the arteries and capillaries may be found distended with blood.

Passive hyperemia is more readily detected in the veins of the membranes than in the cord itself.

Anemia is an important and easily recognized condition. Experimentally, it has frequently been produced by ligation of the abdominal aorta. Cases have, occasionally occurred in human beings in which this vessel was occluded by a thrombus, giving rise to similar changes. The cord, under these circumstances, is somewhat swollen, pale, and soft; not invariably, however, for cases have been reported in which microscopically it was entirely normal. The ganglion-cells, particularly those of the anterior cornua, are most distinctly affected. They exhibit usually the characteristic features of chromolytic degeneration. Similar changes may occur in other portions of the cord, but are exceedingly rare, partly on account of the free anastomosis of the blood-vessels, partly because if, as sometimes happens, thrombi are formed in the vertebral arteries, death occurs before characteristic changes have had time to develop.

Varicose Veins.—Occasionally a group of vessels in one part of the spinal cord will be dilated and varicose, forming a sort of plexiform angioma. Angiomatous formations are frequently observed in various forms of myelitis and sclerosis.

Hemorrhages may be of two kinds: *punctate* and *massive*.

Punctate hemorrhages are really nothing but pericapillary exudations of blood-cells, which can readily be distinguished from the drops of blood that form at the cross-section of blood-vessels by the fact that they cannot be washed off. It is probable that if death does not occur at once they are in great part absorbed, leaving perhaps a minute scar that may be readily overlooked. These minute hemorrhages are perhaps more common in the cervical region than elsewhere. They are found in the course of infectious diseases, particularly those affecting chiefly the nervous system, such as tetanus, and especially hydrophobia. Small agonal hemorrhages into the substance of the spinal cord, particularly in the region of the central canal, are not uncommon. Occasionally these may be visible to the naked eye; they are, of course, to be distinguished from antemortem changes by the regular form of the blood-cells and the absence of blood-pigment. They are only important on account of the possibility of their being mistaken for pathological changes.

Massive hemorrhages may be infiltrating or circumscribed. In the former the blood is found between the nerve-fibers and in the meshes of the neuroglia. The nerve substance is usually more or less degener-

ated, and the lesion corresponds anatomically to the hemorrhagic infarct. Circumscribed hemorrhages are usually small when compared to those in the brain, a circumstance due, of course, to the restricted area in which they can occur.

They do damage, of course, at once, by the separation of the fibers and cells; the greater damage, however, results from the pressure of the clot within the closely attached meninges. If the meninges be opened, thus relieving the tension, degeneration is much less apt to occur.

The most common cause of this form of hemorrhage is traumatism, and it may sometimes occur as a result of concussion without fracture of the spinal column. Hemorrhages may also occur in persons with diseased arteries as a result of violent effort or emotional disturbance.

The clots are usually irregularly oval in outline, and are often surrounded by hyperplastic neuroglia, in the midst of which are found compound granular cells, and more or less degenerated nervous tissue.

In the later stages the formation of fibrous tissue is apparent; capillaries may also be found bending into the substance of the clot, which eventually is absorbed, leaving a scar that nearly always contains some pigment surrounded by coarse-meshed neuroglia tissue. Rarely the pigment is absorbed and a cyst remains. Occasionally the hemorrhagic focus is restricted to the gray substance, the blood being found in cylindrical masses. This arrangement is due to the fact that in normal circumstances the gray matter is softer than the white, and offers less resistance to the extravasation of the blood. In this case the infiltrated area soon becomes filled with granular cells, the nerve-fibers degenerate, and crystals of hematoidin appear.

Hematomyelia.—If the central canal is dilated and contains blood, the condition is known as hematomyelia. This may occur as the result of traumatism or because of some vascular degeneration. The latter form is occasionally associated with syringomyelia, and is found most frequently in the cervical portion of the cord. If the hemorrhage occurred some time before death, the only traces that persist will be discoloration of the ependyma, and perhaps the adjacent tissue. Hemorrhage may also occur during the death agony, in which case the central canal may either be filled with normal blood-cells, or, if it is at all dilated, there will be a thin layer of blood-cells upon the surface. The most common situation is at the point where the central canal opens into the fourth ventricle.

INFLAMMATION

Myelitis, in the strict sense, is a term signifying an inflammation of the substance of the spinal cord. According to this view, it should be limited exclusively to forms of spinal disease secondary to haematogenous infection, extension from the pia, or possibly extension from the central canal, although the latter can be dismissed as an unknown variety. The name has been used, however, to signify any form of softening that may occur, whether it be produced by injury or disease of the spinal column, by tumors, or by poisons circulating in the blood.

It has also been applied to secondary changes the result of meningitis and to obscure lesions that either commence with a proliferation of the neuroglia, or as a primary degeneration or atrophy of the nerve substance and secondary increase in the neuroglia tissue. According to the distribution of the lesions, myelitis is spoken of as circumscribed, transverse, or disseminated.

Hematogenous Purulent Myelitis.—As a rule, the membranes of the brain are also infected, and show the characteristic appearances of acute leptomeningitis, with subarachnoid accumulations of pus and injection of the vessels. Cross-section of the cord shows here and there small reddish or yellowish areas distributed irregularly throughout the cord; in longitudinal sections these usually appear as streaks following the course of the blood-vessels. The cord often seems to be softer and may be darker than normal. The microscopical changes consist of accumulations of pus in the pia mater and distention of the vessels, the presence of a perivascular round-cell infiltration, slight degeneration of the nervous tissue in the neighborhood of the lesions, and alteration of the neuroglia, which may show some looseness of its fibers. Alterations may be seen in the ganglion-cells, which consist chiefly of irregularity in the arrangement of the chromophilic bodies and perhaps somewhat diffuse staining. Should, however, ganglion-cells lie in the midst of, or very close to, the purulent focus, they show a severer type of degeneration and often lose their protoplasmic processes. In these cases micro-organisms are not infrequently found.

Myelitis secondary to purulent leptomeningitis is not greatly dissimilar from this, excepting that there is generally a more marked degeneration in the periphery of the cord. The neuroglia cells are increased in this region; there are often minute hemorrhagic foci, and occasionally small peripheral accumulations of pus. These lesions have been observed, particularly by Councilmann, in epidemic cerebrospinal meningitis.

Transverse myelitis, without local foci, secondary to injury or infectious disease—that is, the condition generally denominated myelitis—presents three stages—the stage of red softening, of yellow softening, and of gray degeneration. In the first the membranes of the cord are usually somewhat opaque. The substance of the cord itself may be either swollen or shrunken, and is softer than normal in consistency. Upon section of the cord the surface is seen to be pink, and there may be minute hemorrhages; the tissue swells so that the surface of the cross-section is slightly convex. Microscopically, the most characteristic feature is the congestion of the blood-vessels; this is more marked in the veins than in the arteries. There is usually a considerable amount of perivascular cellular exudate, the majority of these cells being polynuclear leukocytes. The myelin-sheaths show here and there degeneration; the axis-cylinders are swollen, granular, and somewhat shrunken. The neuroglia cells are sometimes swollen, sometimes irregular in outline and increased in number. The neuroglia fibers in the neighborhood of the vessels form a loose, irregular network. The ganglion-cells show

pronounced alterations, usually similar to those already described as occurring in intoxication, such as irregularity in staining, peripheral situation of the nucleus, and varicosity or fragmentation of the protoplasmic processes. If the process has lasted any considerable time, the most characteristic feature of myelitis, namely, the accumulations of granular cells, begins to take place. It is not certain what these cells are, but in all probability they represent the wandering connective-tissue corpuscles that have absorbed the granular fatty detritus of the myelin fibers. Occasionally, hyaloid bodies are present, even in considerable numbers. These are more irregular in outline than those seen in more chronic conditions, and, according to Leyden and Goldscheider, are probably due to coagulation of an inflammatory exudate. In the next stage a pressure-anemia begins to be apparent. A cross-section through the freshly removed cord shows that it is still somewhat swollen; the color is yellow. The distinction between the gray and the white matter is preserved, but the gray matter is distinctly shrunken. Microscopically, the blood-vessels are shrunken; the perivascular cellular exudate is still present, but many of the cells contain fat-droplets. Throughout the whole cord are found compound granular cells, giving to it a peculiar and characteristic appearance. The nerve-fibers are swollen, granular, or shrunken. The myelin-sheaths are filled with droplets of fat, or have partially disappeared. The neuroglia may be still looser in its texture. The neuroglia cells are more apt to show degenerative changes. In this stage the alterations in the ganglion-cells are extreme. They may be swollen and irregular; often they form irregular, vacuolar-looking masses; some, however, are shrunken, stain dark, and exhibit no trace of a nucleus. Others may perhaps be still recognized by the presence of a small vesicle containing the peculiar brownish pigment, and finally it is evident that some have wholly disappeared, because the number is much less than normal. In the severest grades of this condition the substance of the cord has undergone liquefaction and is reduced to a puriform mass, which it is impossible to examine, excepting upon films. It is then found to contain fat-droplets, granular cells, and detritus. In the stage of gray degeneration there is a secondary distention of the blood-vessels, giving it a somewhat redder appearance. There is proliferation of the connective tissue, which has a tendency to retract and cause concavity of the surface of the section. The granular cells are found chiefly in the neighborhood of the blood-vessels. The neuroglia tissue is looser and appears to enclose numerous vacuoles. The nerve-fibers have in large part disappeared, although a few show degenerative changes, and the ganglion-cells are reduced to a few masses of pigment or else have disappeared entirely. After the cord has hardened, as occurs sometimes in various forms of sclerosis, cracks may appear in its substance from the retraction of the connective tissue. By this time secondary degenerations usually begin to appear above and below the lesion, particularly in the sections stained by Marchi's method.

Pressure-myelitis.—The alterations produced in the cord by slowly

developing pressure, such as the growth of a tumor in the membranes, or gradual bending of the spinal canal, as in Pott's disease, produce somewhat characteristic changes. The cord at first becomes anemic, due to the mechanical occlusion of blood-vessels in the affected segment. As the pressure increases and the anemia continues degenerations ensue in the white matter. These are accompanied by the appearance of a moderate number of granular cells and by slight proliferation of the neuroglia. It appears that this degeneration affects first the myelin-sheaths, and that the axis-cylinders may maintain their vitality for a considerable length of time, for regeneration has occurred after the cord has been considerably reduced in size by long-continued pressure. The gray matter appears to persist for a longer time. This does not mean that the ganglion-cells remain absolutely intact, for in the early stages of the process they exhibit various degenerative changes. As we already know, however, such degenerative changes are not necessarily fatal to the vitality of the cell. Later, they begin to shrink, usually becoming at first darker, then losing their protoplasmic processes, and ultimately undergoing change into small irregular vesicles that are frequently pigmented. The neuroglia gradually proliferates, and ultimately the cord is converted into a sclerotic mass at the point of pressure. This mass is gray in color, seems dry, and often in the process of hardening develops numerous irregular fissures. The central canal is variously affected. It may be, at different levels, obliterated, dilated, doubled, or even tripled. This appearance of doubling or tripling, however, is due to the extrusion of diverticula, which pass upward or downward more or less parallel to the axis of the cord. The epithelium lining the central canal maintains its vitality to a remarkable degree, and, even when all other nervous structures have disappeared, stains distinctly and is of normal shape. Frequently the endothelium lining the under surface of the pia, or the lymph-channels arising from it, proliferate to a remarkable degree, and large masses of endothelial cells may be found either immediately beneath the pia or more deeply situated in the substance of the cord. In some cases this appears to be almost a tumor formation. Secondary degenerations, of course, occur as soon as the axis-cylinders begin to swell, and are identical with those found in other complete transverse lesions.

Acute Anterior Poliomyelitis.—In this disease, clinically designated infantile palsy, the ganglion-cells of the anterior cornua of the spinal cord, their neuraxons passing out through the anterior roots, and the muscles over which they have trophic influence, are the principal parts involved. The disease is undoubtedly due to hematogenous intoxication or infection. It develops after exposure to cold, subsequent to some other infectious disease, such as scarlet fever or measles, and occasionally has appeared as an epidemic. Children are almost exclusively affected, usually about the period of the second dentition, except in the epidemic form, when any age is liable to an attack. The nature of the poison that causes it is unknown. (See chapter on Filterable Viruses.)

Macroscopically the cord presents no characteristic external alterations. If section is made through the diseased portion, it can be seen that the tissues of the cord are somewhat redder than normal, particularly the anterior cornua of the gray matter, and minute hemorrhages may also be observed in this region. The tissue is somewhat softer than normal, and the blood-vessels are considerably distended. In old cases—that is, those with changes consecutive to the cessation of the acute process—the cord may be smaller and somewhat denser. Upon section it is readily observed that one or both of the anterior cornua are considerably reduced in size. The anterior roots from the diseased area may be considerably shrunken and fibrous. Microscopically, in the early stages the most striking appearance is that presented by the blood-vessels. These are greatly distended and surrounded by a wall of round cells. The vessels in the gray matter of the anterior cornua, in the anterior commissure, and in the anterior septum appear to be chiefly involved. The posterior half of the cord presents few, if any, alterations. The neuroglial tissue seems to be somewhat looser, and throughout all the affected tissue there is more or less mononuclear cellular infiltration. The ganglion-cells are much altered. They may be swollen and colorless, the chromatin granules may be arranged in irregular masses, the processes are irregular, the nucleus may stain diffusely, and the nucleolus show vacuolar degeneration; the pericellular space is either distended by edema or by mononuclear cells. In all cases there seems to be a primary round-cell infiltration of the pia mater, which also penetrates the cord and follows the connective tissue. In the more advanced stages both nucleus and protoplasmic processes have disappeared, leaving nothing but the thickened axis-cylinder springing from the cell. The perivascular spaces may be somewhat distended, and often contain round cells. Even in cases examined a few days after the onset it is evident that some of the ganglion-cells have degenerated completely and have disappeared, as their number is markedly diminished. The fibers of the anterior roots show the ordinary forms of degeneration, the presence of globules of fat in the sheaths, and swelling or fragmentation of the axis-cylinders. The affected muscles very early exhibit fatty degeneration and atrophy of the fibers. In cases examined several months after onset considerable atrophy has usually taken place in the anterior horns. The perivascular round-cell infiltration is still very distinct, and usually compound granular cells are found in considerable numbers in the lesions. The ganglion-cells are fewer, and those that remain may be either normal or partially degenerated. Many fibers have disappeared from the anterior roots, and the trophic changes in the muscles are still more pronounced. In those cases examined very late—that is, some years after the development of the process—the anterior horns appear to be markedly diminished in size, although this alteration is exceedingly unequal, often one horn being involved whilst the other is perfectly normal or exhibits only slight alterations. Occasionally the anterior horns appear paler, but of almost normal size, apparently the result of a colloid degeneration of the neuroglia tissues.

The blood-vessels are dilated and their walls thickened, and they may contain some cellular infiltration. In those parts where the process is most severe all the ganglion-cells have disappeared; in others a few may remain, and these are usually normal. The neuroglia has undergone hyperplasia, and consists of a coarse meshwork containing many nuclei. The medullated fibers of the anterior roots are partially or completely destroyed. Degeneration of the medullated fibers of the pyramidal tract may sometimes be traced for a few segments above the affected region; as a rule, it is slight, and involves only a few of the fibers. The lesions usually attack several segments of the cord, and are most frequent in the lumbar region, although any part may be affected, even the cells of the medulla.

The pathogenesis of the disease cannot be said to be settled, but it seems that virus arrives in the spinal cord by way of the anterior spinal artery and its accompanying lymph-channels. Within the cord it seems probable that spread occurs along the lymphatics.

The clinical course of the disease is sufficient evidence of the fact that at least some of the cells recover their functions completely. After the paralysis has reached its greatest extent a very considerable degree of recovery may ensue, and only certain groups of muscles remain affected. Some of these degenerate and contract, giving rise to various deformities in the limbs.

Landry's ascending paralysis is an acute spreading general muscular palsy due usually to an ascending myelitis, alone or combined with degenerative peripheral neuritis. The histological change in the cord may be that of poliomyelitis or a total ascending myelitis. The disease appears as a sequel to some of the acute infections, such as enteric fever, or without apparent antecedent cause; for such attacks many bacteria have been held responsible, but the cause is not yet settled. During an epidemic of poliomyelitis it is common to meet ascending and fulminating cases of the Landry type.

Inflammation of this class, that is, chiefly affecting the motor cells, may either ascend to or primarily involve the bulb or basal ganglia and cause *superior poliomyelitis* or *polio-encephalitis*. Pathologically the changes are the same, but there is relatively less tendency to gross degenerations. The lesions affect, of course, the ganglia of the cranial nerves. (See Bulbar Palsy.)

Tuberculosis, aside from tuberculous meningomyelitis, is rare, but may occur as miliary tubercles or by coalescing of these into larger granulomata. They cause transverse myelitis. *Syphilis* of the cord is said to appear as an acute degenerative myelitis in the secondary stage, and may occur as secondary to luetic meningitis. The most important results of syphilis are the fibratic and degenerative lesions like tabes.

PRIMARY DEGENERATIONS OF THE CORD

Primary degeneration of the spinal cord is characterized by the more or less complete destruction of certain systems of fibers, affecting their

whole length, without solution of continuity in any part of their course or distinct degenerative changes in the ganglion-cells from which they arise. Certain groups of fibers appear to be more frequently affected than others; these are particularly the columns concerned in the conduction of impulses from or to the brain. They may be classified as follows: (1) The sensory neurons of the cord, which are composed of the unipolar cells of the spinal ganglia, and their neuraxons. They pass from the posterior roots into the spinal cord, and enter first the column of Burdach, subsequently bending into the column of Goll, and ending in the nuclei of Goll and Burdach in the medulla. (2) The central motor neurons, commencing in the pyramidal layer of the motor cortex, passing down through the internal capsule, the pyramids, and the pyramidal columns of the cord. (3) The peripheral motor neurons, commencing in the ganglion-cells of the anterior cornua, passing out from the anterior groups, and terminating in the muscles.

The most important primary degeneration is *tabes dorsalis*, or *posterior sclerosis*; it involves almost exclusively the sensory neuron. Involvement of the peripheral motor neuron gives rise to the disease known as *progressive spinal muscular atrophy*; degeneration of both motor neurons, to *amyotrophic lateral sclerosis*.

Posterior Sclerosis

Degeneration of the posterior columns, when occurring independently of distinct lesions of the posterior roots or section of the spinal cord—that is, as a definite form of disease—is known as *tabes dorsalis*, and corresponds clinically to *locomotor ataxia*.

There has been considerable discussion of late years as to whether this is due to systemic disease attacking primarily certain columns or tracts of fibers in the spinal cord, or to a condition secondary to disease of the posterior roots.

Trepinski has combated the latter view, as a result of the comparison of the areas of degeneration in certain cases of locomotor ataxia with the areas of myelination in the cords of human fetuses. He believes that *tabes* is strictly a systemic disease, and Schaffer partially agrees with him. Obersteiner, however, after a careful review of their work, still adheres to the theory that the posterior roots are primarily affected.

The fibers of the posterior roots appear to originate in the spinal ganglia. Upon entering the cord they divide into the ascending and descending branches, both of which give off collaterals. They may be divided into two groups, the lateral and the median bundles. The lateral fibers are somewhat finer and evidently belong embryologically to a different group, because they acquire their myelin-sheaths later and pass directly into the zone of Lissauer, thence into the substantia gelatinosa of Rolando, and some of them terminate in arborization about the cells of the columns of Clarke. The median bundles, which consist of coarser fibers, pass inward, then upward to the inner side of the posterior roots, then bend in and form the columns of Burdach, and, finally, those from the lower regions of the cord enter the columns of Goll and terminate in the nucleus and the medulla. Experimental degeneration caused by section of the posterior roots in animals, or destruction of the posterior roots as a result of pathological processes in human beings, causes ascending degeneration of the posterior columns that corresponds very closely in many respects to the lesions of *tabes dorsalis* (Fig. 433).

Etiology.—It now seems to be well established that syphilis occurs more frequently in the previous history of cases of tabes and of general paresis than in the previous history of other forms of nervous disease. According to various sets of statistics, it varies from 50 to 90 per cent. in all cases (Erb). The theory that syphilis is the important factor in the causation of tabes has received considerable support from the findings of Noguchi. This observer was able to detect the *Spirochæta pallida* in the cord of 12 out of 40 cases of tabes. The Wassermann reaction is positive in a large majority of instances. Nevertheless, a certain number of cases of tabes occur in persons who give no history of syphilis, have never had any symptoms of the disease, and present no signs of it at the time of examination.

Various theories have been suggested to account for the special involvement of the posterior columns. Edinger has suggested that those portions of the central nervous system that are subjected to

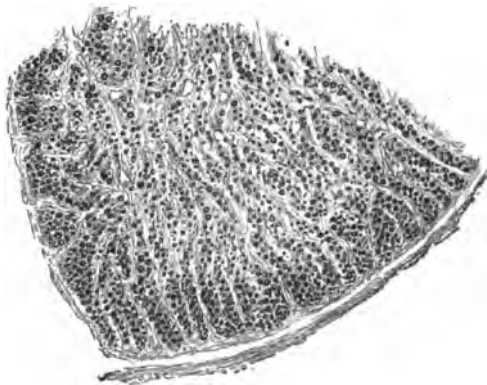


Fig. 433.—Sclerosis of the cord, from a specimen stained by Weigert's method. In the dark area the normal (unaffected) nerve-fibers are deeply stained.

excessive work are more likely than the others to feel the action of any toxin that may exist in the body—such, for example, as the toxin of syphilis. Siebert has slightly modified this theory, suggesting that at the point where the posterior roots enter the spinal cord they are most likely to be subjected to injurious overgrowth of the neuroglia that may be produced by the presence of toxins, exposure to cold, etc. Hitzig believes that toxins may exist in the body for long periods of time, and so alter the blood as to cause it to produce in the more susceptible portions of the nervous system sclerotic changes. Obersteiner has suggested that in all probability tabes is due to a variety of conditions, although he admits that syphilis is by far the most important. As far as we have been able to ascertain, only a single case has been recorded in which injury appears to have been solely responsible for the development of the disease.

Pathological Anatomy.—The macroscopical lesions are as follows: The dura shows no changes; the pia mater in the segment between the

posterior roots is somewhat thickened and opaque, a change which cannot usually be observed in the lateral and anterior regions. The posterior roots may be enlarged. In the advanced cases, however, they seem to be somewhat thinner and more translucent. On section through the cord the gray matter, especially that of the septum and anterior horns, appears to be normal. The anterior and lateral regions of the white matter are similarly intact. In the most advanced cases the white matter between the posterior roots is darker than normal and seems to be shrunken. Its consistency is somewhat softer than that of the normal cord, and the fact that it becomes depressed after section shows that there is some tendency to retraction. In early cases these changes may be slight; in fact, in cords removed from patients suffering from general paresis, in which the earliest stages are usually observed, there may be no macroscopical changes found. In these early stages sections stained by some myelin method exhibit the following changes: In the lumbar region the columns of Goll are degenerated, excepting the anterior portion; in the dorsal region there are usually two areas of degeneration in the column of Burdach; in the cervical region a portion of Goll's column is involved, and there are usually two areas on either side in the column of Burdach near the posterior horns. In nearly all cases there is usually more or less degeneration of the posterior roots. In the more advanced cases the portion of the posterior columns immediately behind the posterior commissure contains normal fibers, but all the rest of the posterior column and Lissauer's zone are degenerated. In the cervical portion the degeneration of the column of Goll is most pronounced, and there is only a small number of normal fibers anteriorly and on either side lying close to the posterior roots. The degeneration extends upward through the medulla as far as the nuclei of Goll and Burdach. It occasionally happens that one portion of the cord seems to be more severely affected than the others; as a general rule, this is the lumbar region or the dorsal and lumbar regions, whilst the cervical portion shows fewer changes. Occasionally, however, the cervical portion of the cord will be particularly involved and the other regions more or less intact. In these cases the columns of Goll show only slight degeneration, whilst in the cervical portion the column of Burdach is markedly degenerated. As the fibers turn toward the center healthy fibers from the posterior roots of the cervical segments are usually less involved, so that the degenerated area lies near the posterior median septum, in the region usually called the middle root-zone. These degenerated areas are characterized by destruction of the myelin-sheaths and the axis-cylinders, their places being taken by proliferated neuroglia, which is characterized by the appearance of thicker and somewhat wavy fibers. In the late stages this hyperplastic neuroglia may undergo considerable contraction (Fig. 434). Proliferation of the neuroglia cells may be observed in the earlier stages, but in the later stages this has largely disappeared. The degeneration of the fibers is in all respects similar to that of the ordinary secondary degeneration. Accumulation of the peculiar amyloid bodies

is usually observed. The gray matter of the cord is little affected, the cells in particular rarely showing distinct traces of degeneration. The fibers that normally pass through the gray matter often disappear completely. This is true especially of the fine fibers of Lissauer's zone and those that form the plexus around the cells of the column of Clarke. The reflex collaterals also frequently disappear, and this is supposed to explain the loss of the reflexes, which is a common symptom of the disease. The vessels usually exhibit some thickening of the adventitia, and occasionally an accumulation of granular cells either in the adventitia or beneath the ependyma. Hyaline degeneration is found occasionally. The pia mater, corresponding to its macroscopical appearance, shows some thickening of the fibers, although this is absent in the earlier cases.

The most interesting subject connected with this disease is the condition of the peripheral nerves, the spinal ganglia, and the posterior



Fig. 434.—Sclerotic and contracted posterior columns in posterior sclerosis (Karg and Schmori).

roots. Degeneration of the peripheral cutaneous nerves is frequently observed, the changes consisting of thickening of the perineurium and the connective-tissue trabeculae, more or less degeneration of the myelin-sheaths, and occasionally swelling of the axis-cylinders.

The results of the examination of the spinal ganglia have been very contradictory, and some authors find them intact, while others describe contraction and irregularity in the outlines of the cells. In no case, however, have the changes been sufficiently pronounced to account for the extensive degeneration in the posterior columns. The posterior roots are invariably degenerated. Some of the fibers are completely destroyed, others show disappearance of the myelin-sheaths and alteration of the axis-cylinders. Nageotte claims to have discovered a round-

cell infiltration in the membranes surrounding the roots that causes a pressure degeneration. Redlich and Obersteiner believe that the changes are most marked after the entrance of the fibers into the cord, and explain this by supposing that there has been a slight constriction at the point where they pierce the pia mater. In this region there is certainly often considerable disappearance of the myelin-sheaths, but it cannot be said positively whether the intramedullary portion of the posterior roots is more degenerated than the extramedullary.

Friedreich's Ataxia

Friedreich's ataxia is a disease characterized by inco-ordination of the gait, the first symptoms coming on usually during puberty. It belongs to the hereditary type of diseases, occurs in successive generations of the same family, and appears to have no other causation. The most constant change is hypoplasia of the spinal cord. This hypoplasia may be regular, so that the whole cord is three-fourths or even less of its normal diameter, or it may seem irregular in the latter instance, being, perhaps, more pronounced in the cervical and upper dorsal regions. Hypoplasia of the cerebellum is a frequent associated lesion. The two conditions are, however, rarely equal, and, according as one or the other preponderates, Marie described spinal and cerebellar forms of hereditary ataxia. The next most common lesion is degeneration in the posterior columns. This is particularly marked in the column of Goll, but, in severe cases, may also involve the column of Burdach. No degeneration at all may be found; such a case has been reported by Nonne; but in these instances the larger fibers are usually absent. Degeneration in Clarke's columns is not uncommon. In regard to the degenerative areas found in the lateral columns there is much difference of opinion. The majority of authors believe that they represent degeneration of the pyramidal columns, although it is certain that none of the clinical symptoms associated with this lesion are present. The degeneration is usually most pronounced in the lower part of the cord, diminishes in intensity upward, and disappears near the normal decussation of the pyramidal columns. According to Marie, the degenerated areas usually lie to the outer side of the normal situation of the pyramidal columns. In all these degenerated areas there is considerable proliferation of the neuroglia tissue, the fibers being especially increased, indicating the likelihood that the change is secondary. Other secondary changes are the thickening and partial adhesion of the pia mater, particularly that part in contact with the posterior columns of the spinal cord, and also the thickening of the walls of the blood-vessels, such as is usually found in sclerotic nervous tissue. Degeneration is also found in the posterior roots, which are smaller than normal. In regard to the condition of the peripheral nerves there is some difference of opinion, but it seems certain that, in some cases at least, there is a degeneration of the sensory fibers. The disease partakes, therefore, of the nature of a combined sclerosis. Some authors hold that it is

due primarily to a hypoplasia of the third primary vesicle and of the neural canal—that is to say, the medulla, cerebellum, and cord. The disease, however, appears to be slowly progressive, and it is not evident in infancy. This may be explained by assuming that the hypoplastic central nervous system is sufficient for the needs of the child, and that as the organism develops it becomes relatively insufficient. This, however, would not enable us to understand why such extensive secondary degenerations are sometimes present.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a disease which, theoretically, should present the following pathological changes: Degeneration in the pyramidal columns, atrophy of the ganglion-cells of the anterior cornua,



Fig. 435.—Multiple sclerosis. Second cervical cord. The spinal roots stain well and are not affected by the disease.



Fig. 436.—Optic nerve, showing degeneration in central parts. (Photographs from the case illustrated in Fig. 437.)

degeneration of the nerve-fibers in the anterior roots and of the motor fibers in the peripheral nerves, and degenerative atrophy of the muscles. The lesions that are actually found, however, are very various. Common to almost all cases is the atrophy of the motor cells of the spinal cord and

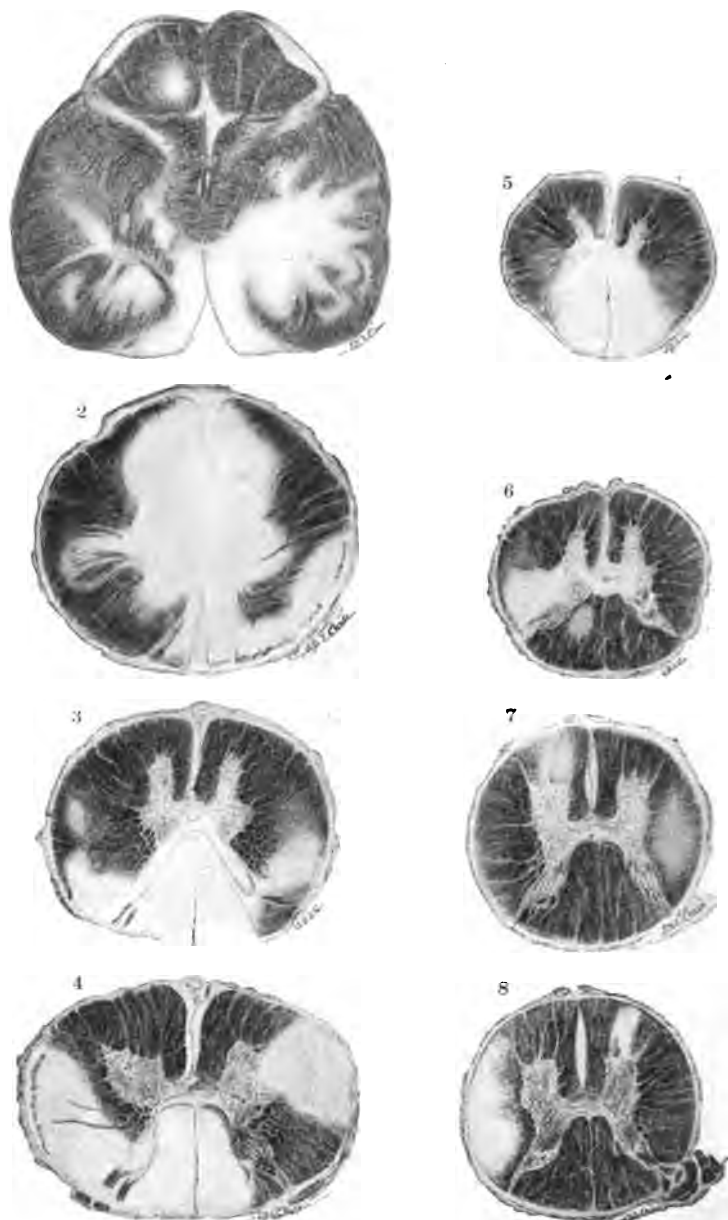


Fig. 437.—Transverse sections of the medulla and cord from a case of multiple sclerosis. Stained by Weigert's method. (Normal tissue colored dark, degenerated areas white.) 1. Medulla. 2. Lower medulla. 3. Third cervical. 4. Fifth cervical. 5. Second dorsal. 6. Sixth dorsal. 7. Twelfth dorsal. 8. First lumbar. The irregular areas of degeneration in different segments of the cord are not associated with secondary degeneration below or above the different lesions, except the degeneration in the posterior columns from the second dorsal up to the medulla (Burr and McCarthy).

degeneration of their neuraxons, and the presence of compound granular cells, but there is no other sign of inflammatory reaction. The degeneration of the ganglion-cells is usually extensive, and the muscles exhibit the changes characteristic of progressive spinal muscular atrophy—that is, swelling of the fibers, increase of the number of the nuclei, indistinctness of the striation, and increase in the amount of connective tissue, with, in the later stages, extreme atrophy of the fibers. The degree to which the pyramidal columns are affected is not constant; at times the degeneration is pronounced and extends as far as the internal capsule. Indeed, distinct alterations have been reported in the motor cortex of the brain—that is to say, degeneration of the ganglion-cells and the presence, in more or less considerable number, of compound granular cells. In other cases the degeneration may cease at a lower point, and in at least one case was not found at all. It has been supposed that in such cases there is only a slight alteration in the nutrition of the ganglion-cells, and that the degenerative changes commence at the peripheral portion of the neuraxon and advance cellipetally. The changes found in the pyramidal columns are, of course, similar to those occurring in the other primary degenerations.

Chronic anterior poliomyelitis, or progressive spinal muscular atrophy, is strictly a degeneration of the peripheral motor neuron, and often appears to be hereditary in character. Otherwise no satisfactory etiology has ever been determined. It is characterized by gradual atrophy of the ganglion-cells of the anterior cornua and by diminution of the size of the cornua themselves. No lesions that distinctly indicate the existence of an inflammatory process are present. The cells gradually grow smaller, become pigmented, and may ultimately disappear. There is degeneration of the fibers in the anterior roots and degenerative atrophy of the muscles. The clinical course is slowly but irregularly progressive. The condition in many respects resembles amyotrophic lateral sclerosis, and cases have been recorded in which other degenerations were found, particularly in Clarke's column and in the posterior columns. The lesions apparently commence in the cervical region, and may later extend to other parts of the cord, and even to the motor nuclei of the medulla. This last causes so-called *bulbar*, or *glossio-labiolaryngeal palsy*, which follows the clinical and pathological characters of the rest of these affections with limitation of the lesions to the medulla, with perhaps an added degeneration of the pyramidal tracts. There is a form of chronic poliomyelitis in which distinct lesions of the vessels are present, and which is apparently only a slow form of the ordinary acute poliomyelitis.

Combined sclerosis, giving rise to ataxic paraplegia, has been described in a great number of instances, and a characteristic symptomatology has been ascribed to the condition. Usually the parts affected are the posterior columns, the columns of Clarke, and, in part, the lateral pyramidal tracts. The lesions do not differ in appearance from those of the other forms of primary degeneration. The areas are gray, somewhat shrunken, and contain an excess of neuroglia, granular cells, and

amyloid bodies. The nature of the process is still undecided. The frequency with which a certain definite combination occurs has led some neuropathologists to believe that it is a morbid entity. Others, however, contend that the parts of the cord affected are those least able, on account of their poor blood-supply, to resist noxious influences, and that, therefore, the disease is only the reaction of the weaker parts of the spinal cord to a general morbid agent. The disseminated or multiple sclerosis are commonly associated with similar lesions in the brain, and have been described under that heading (p. 915).

Lateral sclerosis, with exclusive involvement of the lateral columns connected with the motor cortex or upper neuron, is very rare in a pure form. There is retained muscle tone because the trophic cells in the gray matter of the cord are not attacked. At first there is spasticity and, later, paralysis of the affected muscles.

Degenerations in the white matter of the spinal cord have been described in various forms of chronic anemia, especially pernicious anemia. Two varieties can be distinguished, those in which the areas of sclerosis are disseminated irregularly through the cord, and those

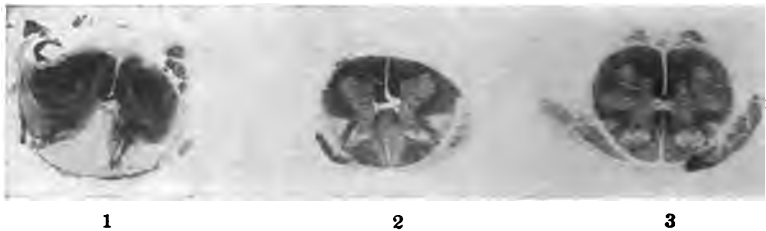


Fig. 438.—Sections from a case of ataxic paraplegia, showing system degeneration of the posterior column, lateral (crossed), pyramidal, and direct cerebellar tract: 1, Cervical; 2, lumbar; 3, sacral (Burr and McCarthy).

in which the degeneration is systemic in nature and follows more or less closely the area of distribution of the fibers of the posterior root. In the latter case the posterior columns are affected most severely, and the lesions are most pronounced in the cervical region. Degeneration, however, may also be found in the lateral columns, either involving only a small patch of fibers, or so extensive as to give rise to the appearance of combined sclerosis. The degeneration appears to occur primarily in the nerve-fibers, with secondary proliferation of the neuroglia. Vascular changes, particularly minute hemorrhages and thickening of the vessel walls, are also found, and when present the nerve-fibers in the immediate vicinity of the vessels are often degenerated. These changes are not, however, found in all cases of progressive pernicious anemia, a number of cases being now on record in which the spinal cord showed no trace of degeneration. No satisfactory explanation has hitherto been given to account for them. It has been suggested that the anemias with spinal lesions belong to a different group, but this is, of course, a mere hypothesis. The absence of degeneration in the posterior roots seems to exclude a peripheral neuritis, although it is possible that in

case of slight disease of a spinal ganglion the terminations of its nerve-fibers in the medulla would exhibit the first trace of degeneration, and this, in fact, corresponds with the condition found in some of the cases.

Similar changes have also been found in other conditions, especially the chronic cachexias, such as tuberculosis, diabetes, and carcinoma. Changes occurring in the spinal cord in ergotism and pellagra have been described. In the former the areas of degeneration are said to be chiefly in the posterior columns, limited, excepting in the cervical regions, to Burdach's column, and there are lesions in the posterior roots. In

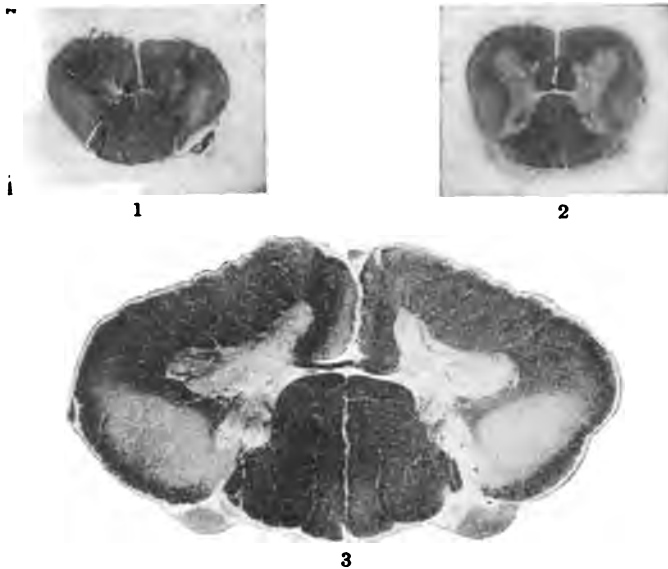


Fig. 439.—Descending degeneration of direct and crossed pyramidal tracts following hemorrhage into the medulla: 1, Dorsal region; 2, lumbar region; 3, cervical region (McCarthy and Pearce).

The lesions presented in the above sections are confined to the motor system, and caused a spastic type of paralysis without sensory derangement.

pellagra degeneration is found in Goll's column, particularly in Burdach's column, and usually in the lateral columns also. There are also partial disappearance of the cells of the anterior cornua and small degenerative foci in the anterior columns. Changes limited to the posterior column have also been noted after diphtheria and leprosy. In old age small, irregular areas of degeneration, particularly in the posterior median column, and sometimes at the periphery of the spinal cord, may be observed.

SECONDARY DEGENERATIONS OF THE CORD

Secondary degenerations of the spinal cord occur after any lesion interrupting the course of one or more of the columns of fibers, and also after any disease of the ganglion-cells that nourish these fibers. They



1. Degeneration of the posterior columns in pernicious anemia.



2. Diffuse anteroposterior and lateral degeneration of cord in a senile case of progressive pernicious anemia.



3. Diffuse degeneration of cord in intense anemia associated with chronic parenchymatous nephritis (cervical cord).

Fig. 440, 1, 2, and 3 present the diffuse toxic lesions met with in anemic and cachectic conditions. The degeneration is diffuse, not confined to any particular tract of the cord, but usually predominating in the posterolateral areas. It is not infrequently referred to as posterolateral sclerosis. No. 1 is from an early case, and shows the relation of the degeneration to the arterial supply of the posterior columns.

have been divided into ascending and descending, according to the direction in which the degeneration proceeds. It will be clear from the description already given of the course of the columns of the cord that the chief variety of descending degeneration will be that of the pyramidal columns. This may occur as a result of injury to the motor cortex, or of interruption of the motor fibers in any part of their course from the cortex to the conus terminalis. If the lesion is unilateral and above the decussation, ordinarily only one pyramidal column is distinctly affected—that is to say, the anterior pyramidal tract of the same side and the lateral pyramidal tract of the opposite side. Careful microscopical investigations, however, have shown that certain fibers that do not decussate pass down the spinal cord in the lateral columns. In

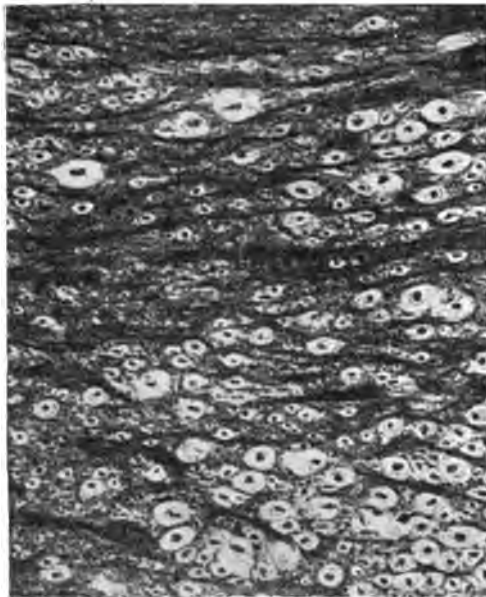


Fig. 441.—Sclerosis of the white substance of the cord.

cases of long-standing secondary degeneration of the pyramidal columns a certain amount of simple atrophy of the ganglion-cells of the anterior cornua has been observed. Descending degeneration has also been observed in the posterior columns. In the upper portion of the cord it assumes the form of two small areas that project from a point slightly posterior to the gray commissure and extend backward and outward. This has been called the comma degeneration of Schultze. In the lower part of the cord these descending fibers appear to approach the posterior commissure and form the oval field of Flechsig. Descending degeneration for a short distance below a total transverse lesion may be found in all the columns. Ascending degeneration occurs chiefly in the posterior columns, and is described in connection with *tabes dorsalis*. In

case of isolated injury to one of the posterior roots, there may be traced upward a slender band of degeneration that gradually approaches the posterior septum. Ascending degeneration also occurs in the direct

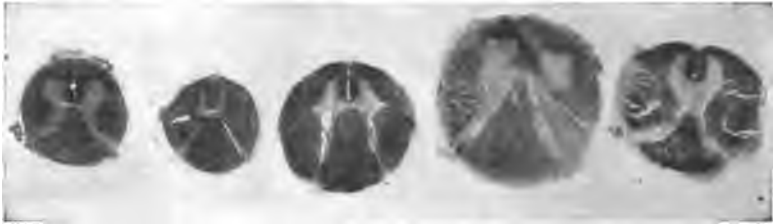


Fig. 442.—Acute gliomatous degeneration of the spinal cord, showing relative size of cord in different localities.

cerebellar tract, and may often be found to be associated with disease of the ganglion-cells in Clarke's columns. It extends as far as the restiform bodies in the medulla. Ascending degeneration also occurs



Fig. 443.—Highly magnified section of the cord from the same case. The white areas correspond to an active proliferation of the neuroglia cells with destruction of the myelin-sheaths. The neuroglia cells act as scavenger cells in this destructive process. There was no secondary degeneration below the cervical cord. The disease ran an acute course and presented an ascending type of paralysis (McCarthy and Pearce).

in the anterolateral tract of Gowers. After total transverse lesion secondary alterations may usually be detected in the remote portions of the cord in the course of from five to seven days. These alterations

consist of a swelling of the axis-cylinders and, within a very short time, fatty degeneration of the myelin-sheaths. Granular cells appear early in the tissue. In the course of a month the degenerative changes are quite pronounced, and may readily be detected by Weigert's method. The myelin-sheaths have disappeared wholly or in part; the axis-cylinders have also vanished, although some varicose fibers may be found here and there in the lesion. Compound granular cells largely fill the field, but there is also a distinct hyperplasia of the neuroglia tissue, giving the area, macroscopically, a somewhat grayish appearance. Still later, contraction begins to occur and the appearances seen in the primary degenerations are found.

TUMORS

Glioma.—Of the primary tumors of the spinal cord, the most frequent and important is glioma. This is usually infiltrating in type and elongated, extending for a distance of several segments along the cord, and sometimes involving the nerve-roots, causing them to swell and become harder. It may give rise to curious distortions in shape, and an apparent hypertrophy; this latter is probably the result of the compression in a longitudinal direction of some portion of the cord, so that in a given section more ganglion-cells are found than would normally be present.

Proliferation of the neuroglial tissue of the cord, causing increase in size of the segments affected—often without, however, distinctly injuring the normal tissue of the cord—may be produced by pressure on the outside or by interference with the circulation. It occurs in cases of tumor of the membranes or of the spinal column, in disease of the spinal column, and in pachymeningitis. The neuroglia tissue frequently contains, in addition to the increase in the number of fibers, huge multipolar cells that have been described in true gliomata by Stroebe.

Sarcoma alone, or containing gliomatous or mucoid tissue, or of the type known as angiosarcoma, may also appear.

Carcinoma and sarcoma may also appear as metastatic growths.

Cysts are exceedingly rare, but both the echinococcus and the *Cysticercus cellulosæ* have been reported.

CHAPTER XIV

DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

THE GANGLIA OF THE CRANIAL AND SPINAL NERVES

THE ganglia of the spinal nerves may be diseased as a result of extension of pathological processes, usually tuberculosis, from the surrounding bony structures. It is probable that they are also subject to inflammatory changes. Spiller and Keen have reported the results of the examination of a number of Gasserian ganglia removed on account of persistent trifacial neuralgia, in which they found degeneration—in some cases total—of the myelin-sheaths and the nerve-fibers in the ganglia. In one case the degenerated nerve tissue was replaced by connective tissue, giving rise to marked sclerosis. Occasionally the cells in the ganglia had undergone atrophy, and in all instances the vessels were distinctly sclerotic, the lumen being sometimes completely obliterated. The authors believe that these changes are not primary, but secondary to lesions in the peripheral sensory nerves.

The spinal ganglia may also be diseased. Slight degenerative changes have been noted in locomotor ataxia and as a result of peripheral neuritis. In this case the walls of the ganglia show swelling and granulation of the chromatin bodies, and are often somewhat shrunken. More frequently the ganglia are involved as a result of disease of the surrounding bones; particularly caries or sarcoma of the spine may produce pressure, resulting in atrophy, or, in the case of the former, areas of tuberculous softening. The ganglia of the spinal nerves are sometimes found diseased in cases of herpes zoster, and are supposed to have an etiological relation to that disease. Zinno has reported a case in which there appears to have been a chronic swelling of the ganglia, some of which were as large as a pigeon's egg, as a result of a hyperplasia of the neuroglia and the connective tissue. These swollen ganglia pressed upon the cord and produced secondary degenerations. Enlarged spinal ganglia have also been observed in acromegaly.

THE NERVES

CIRCULATORY DISTURBANCES

Hyperemia of the nerve-trunks attends acute inflammations. The vessels of the perineurium may be intensely injected.

Hemorrhages may result from acute congestion or from traumatic injuries. They take the form of punctate ecchymoses in the perineurium or endoneurium.

Edema of the nerve-trunks may occur in the nerves traversing areas of inflammation.

ATROPHY AND DEGENERATION

Atrophy of the nerves occurs in consequence of pressure upon the nerve or as a result of disease (*neuritis*) of the nerves. It may also result from disease of the central nervous system, causing disturbance or destruction of the nuclei of origin of the peripheral nerves. Occasionally atrophy arises without definite cause in old age. The changes in the nerve are similar to those following section of the nerve, and are described under the heading Degeneration.

Degeneration.—Injury of a nerve in its course produces various manifestations in the nerve-fibers corresponding more or less to the nature of the destructive agencies. It is obvious that if the nerve be divided by a clean incision, the degenerative changes below the point of incision will be less extensive than if the destructive agent is severe, such as in cauterization, the crushing of the nerve-trunk with extensive disintegration, or the removal of a section of some length. Still milder changes, however, may be produced by a ligature that is not drawn tightly enough to destroy completely all the nerve-fibers. Degenerative changes are less pronounced if there is prompt coaptation of the injured ends, or if the continuity of the nerve is not entirely destroyed.

If a nerve is examined immediately after injury, there will be found only deformity of the nerve-fibers. This consists in dislocation of the myelin and perhaps fibrillation of the axis-cylinder, so that it seems to be crushed into and diffused throughout the white substance of the nerve-fiber. Within a few hours the cells in the myelin-sheath begin to exhibit signs of degeneration, the chromatin swells, stains more feebly, and may undergo fragmentation. At the end of eighteen hours the axis-cylinder is usually slightly swollen and its outline becomes irregular. These changes, however, are by no means uniform throughout the whole nerve, some parts perhaps being almost normal and others extensively degenerated. At the end of thirty-six hours the myelin substance has undergone fatty degeneration, with the formation of small globules. These changes are found on both sides of the lesion, on the proximal side extending to the first node of Ranvier, and on the peripheral side extending considerably beyond this. At first the changes in both fragments are approximately equal, but those in the peripheral end rapidly progress and soon dominate the field. The changes in the peripheral fragment, however, are more pronounced near the lesion and diminish toward the periphery. In the central end there are nearly always a few fibers that degenerate as far as the spinal cord, but these are the exception.

REGENERATION AFTER INJURY OF A NERVE

The first sign of regeneration is proliferation of the cells of the sheaths. Their nuclei exhibit karyokinetic figures, and there appears to be an increase in their protoplasmic substance. At the same time the cells of the connective tissue also undergo multiplication and, to a certain extent, act as phagocytes, absorbing the fatty detritus. The

protoplasm of the cells of the sheath gradually elongates and occupies the situation of the myelin substance and the old axis-cylinder. There appears to be some doubt whether these changes are more pronounced in the proximal or distal fragments; at any rate, the protoplasm of the cells of the sheaths on both sides of the lesion seem to possess phagocytic properties and to absorb some of the fat and detritus resulting from the degenerative changes. The protoplasmic mass usually closes the free ends of the nerve-fibers, and assumes a somewhat conical form, not unlike a node of Ranvier. This mass appears to be continuous with the partially degenerated end of the axis-cylinder. Toward the end of the first week the elongated protoplasmic masses in the end of the nerve-fibers become somewhat differentiated. In the interior may be seen a delicate fibrillated structure that appears to be continuous with the axis-cylinder of the nerve; outside of this is a delicate membrane, but both of these structures lie within the old myelin-sheath, in as far as it is preserved. It is probable that mildly damaged axis-cylinders, or those with a moderate grade of chromatolysis, can regenerate, but when the injury is severe or the nerve-fiber completely severed and separated it is not likely that union of the segments results. Both the proximal and peripheral fragments of the axis-cylinder degenerate and a new one must grow from the cell. Axis-cylinder regeneration must, of course, be preceded or accompanied by processes in the sheath and neurilemma. As the new nerve-fibers increase in length they gradually pass through the injured area and come in contact with the proximal area of the peripheral fragment. In this the cells of the sheath have undergone proliferation and have formed protoplasmic masses at the ends of the fiber. Differentiation in this protoplasmic mass does not, however, appear to occur until the new axis-cylinder reaches it. Gradually the nerve approximates more and more closely to the normal appearance, the axis-cylinder becoming more distinct and the myelin-sheath thicker until it can be said to be re-established. In the course of the absorption of the fatty and other detritus, cells that are filled with fat-droplets accumulate in the connective tissue of the nerve and between the fibers, which are probably ordinary compound granular cells. It is questionable, however, whether they are derived from the endothelium of the lymph-spaces or from the leukocytes, or whether they represent the excess of the proliferated cells of the sheath. Somewhat later, concentric masses may be found that resemble very closely the amyloid or hyaloid bodies of the central nervous system.

INFLAMMATIONS

Neuritis may be either acute or chronic. It has also been classified as parenchymatous and interstitial; the former comprising the degenerations of the nerve-fibers without involvement of the connective tissue, and the latter comprising all those forms associated with the characteristic signs of an inflammatory process in the connective tissue of the nerve.

Acute interstitial inflammation, or neuritis proper, may be caused by direct extension from an inflammatory focus in the surrounding tissue or by trauma, or as the result of some as yet unknown poison which is generally supposed to be rheumatic in nature. It may also

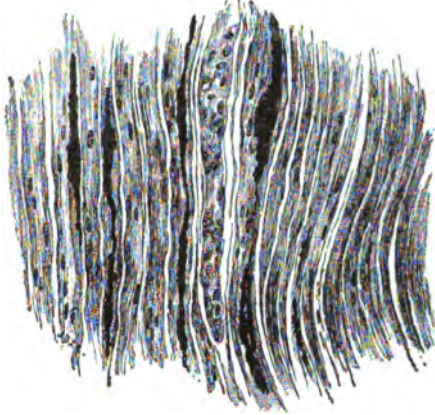


Fig. 444.—Neuritis: longitudinal section, showing degenerated nerve-fibers (black); Azoulay's method; $\times 300$.

occur in the course of acute infectious diseases, or as an independent condition, as in beri-beri. The inflammatory changes occur in the perineurium and the endoneurium. The nerve is swollen, soft, and pinkish in color. Microscopically, both the perineurium and the

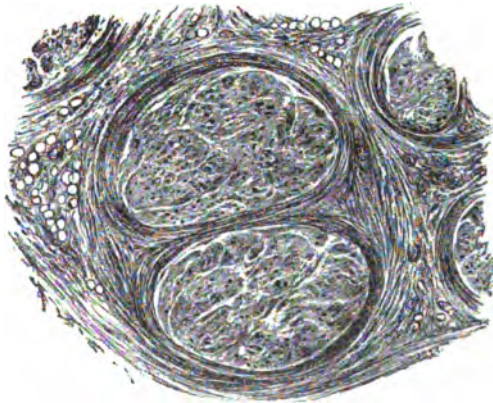


Fig. 445.—Chronic hypertrophic interstitial neuritis; $\times 100$ (case of Dejerine).

trabeculae of connective tissue are increased in size, the blood-vessels are distended, and there is extensive round-cell infiltration. In the acute forms partially degenerated fibers with fatty myelin-sheaths and swollen axis-cylinders are found very early. The primary change unques-

tionably occurs in the connective tissue, and the nerve-fibers are involved secondarily, the myelin-sheaths being the parts first affected.

Chronic interstitial neuritis may follow the acute form or commence as an independent condition. The nerve is harder than normal, the connective tissue is increased, the walls of the blood-vessels are thickened and their lumina may be partially obliterated. More or less round-cell infiltration is found in the hyperplastic connective tissue, and the nerve-fibers show extensive degeneration, many of them having disappeared, and the few that remain presenting marked morbid changes. Often there is a distinct proliferation of the cells in the neurilemma. This form of neuritis in particular is associated with muscular degeneration, and appears to give rise to the type known as the neural form of progressive muscular atrophy. Associated changes are often found in the spinal cord, and consist of an ascending degeneration in the posterior columns and more or less alteration of the ganglion-cells. In a variety of this disease, described by Dejerine under the name of *chronic hypertrophic interstitial neuritis*, there is an actual overgrowth of the connective tissue, the nerve-trunks forming huge, firm cords, several times the normal thickness, that may readily be felt beneath the skin. This disease is apparently due to some hereditary familial influence. Microscopically, the changes consist of an enormous proliferation of the connective tissue with round-cell infiltration, partly about the sclerotic blood-vessels, and pronounced degeneration of the nerve-fibers. The muscles undergo degenerative atrophy, and there are secondary degenerations in the spinal cord.

Suppurative neuritis is nearly always secondary to suppuration in the tissue surrounding the nerve. It is characterized by the presence of small foci of pus in the connective tissue and softening of the nerve-trunk. The nerve-fibers degenerate very rapidly.

Parenchymatous neuritis is characterized by a primary degeneration of the nerve-fibers, the alterations in the connective tissue being secondary. It is always due to some toxic or infectious substance circulating in the fluids of the body. The most common causes are lead, arsenic, alcohol, and diphtheria; but it also occurs as a result of other poisons and infectious diseases, and in the course of tabes dorsalis. The nerve-trunk becomes slighter, firmer, and grayer. Inflammatory changes are slight or absent, while the degeneration of the nerve-fibers is pronounced. Changes have frequently been found in the cells in the anterior cornua of the spinal cord.

Polyn neuritis does not differ from the isolated form, excepting that a number of nerve-trunks in various parts of the body, usually the limbs, are affected at the same time. It is most frequently of the parenchymatous type.

INFECTIOUS DISEASES

Tuberculosis of the nerve-trunks is due to direct extension. It most commonly affects the roots of the nerves, and occurs in the course of tuberculous spinal or cerebral pachymeningitis. The connective tissue

is first affected, and may contain small cheesy foci, in which epithelioid and giant cells are found. The nerve-fibers degenerate secondarily.

Syphilis also occurs, chiefly in the nerve-roots. It causes overgrowth of the connective tissue, particularly in the perineurium, with pressure upon and degeneration of the nerve-fibers. Gummata are sometimes observed upon the cranial nerves.

Leprosy is characterized by the presence, in the connective tissue of the nerve-fibers, of large epithelioid cells containing vacuoles more or less filled with lepra bacilli. The bacilli cause a certain amount of hyperplasia of the connective tissue, which presses upon and eventually destroys the nerve-fibers. The disease affects the small cutaneous nerves almost exclusively, and causes anesthesia and trophic changes in the skin.

TUMORS

Neuroma.—The tumors embraced by this term have been sufficiently described under the heading Neuroma, in Part I.

Sarcoma is a rare tumor of nerve-trunks. It takes its origin from the connective tissues of the nerve.

Muscle-fibers are sometimes found in intramuscular nerve-trunks. They usually exhibit proliferation of the nuclei, but the striations remain distinct. Their position has been ascribed to errors of development, but it is not certain that they are without function.

CHAPTER XV

THE EYE

ANATOMY

The Conjunctiva.—This is a sac lined with stratified epithelium covering the exposed portion of the eyeball and reflected to the lids, at the margin of which it becomes continuous with the skin. When this sac is dissected off and spread out it is as large as the palm of the hand. Upon the inner surface of the lids and upon the ball there is squamous, near the canthus, columnar epithelium. In the latter situation goblet-cells abound. Beneath the epithelium is a loose areolar and adenoid layer and then a thick connective-tissue layer, the so-called tarsal cartilage which contains the Meibomian glands. The subepithelial layer upon both lids and ball is loose but highly vascular.

The lachrymal apparatus consists of a compound racemose gland lying in the upper outer portion of the orbit, discharging tears through two ducts into the lachrymal sac at the internal canthus, by the lachrymal puncta near the caruncle. The tears are expressed from this sac by the contraction of the palpebral sphincter and forced into the nasal duct. They are spread over the conjunctival surface by nictitation.

The cornea is a transparent avascular epithelial structure continuous at its margin with the sclera. From without inward there is first a squamous epithelial layer continuous with the epithelium of the conjunctiva, covering the acellular outer capsule, or Bowman's membrane. The body of the cornea is composed of lamellated epithelium comparable to the horny epidermis, between the layers of which course lymph-channels; the interstitial branched cornea cells lie in lacunæ. A hyaline internal capsule (Descemet's membrane), lined on the surface of the anterior chamber by a single layer of endothelium, constitutes the innermost part of the cornea. The cornea is without blood-vessels, nutrition being derived from vascular plexuses at its juncture with the sclera. The two internal layers join with the structures of the uveal tract.

The sclera is the stiff external capsule of the eyeball, composed of variously arranged bundles of white connective tissue with some yellow elastic fibers.

The lens is a transparent convex epithelial body lying immediately behind the iris, surrounded by an acellular capsule thickest anteriorly. The body is formed of homogeneous fibers which grow from the capsule of the equator and the portions just anterior to this zone, the origin of these fibers being a layer of transparent polygonal cells lying below the lens capsule. The older fibers are pressed toward the center to

form a nucleus. The lens is held in position by fibers from the ciliary body.

The **vitreous humor** is a soft, gelatinous, clear, colorless tissue occupying the center of the inner eye. It contains a few leukocytes and branching cells, the processes of the latter are attached to the delicate vitreous capsule and form the supporting structure.

The **iris, ciliary body, and choroid** form the uveal tract. The first consists of an anterior and posterior layer of endothelium beneath which is a hyaline layer. The endothelium in front is continuous with Descemet's membrane, that posteriorly extends into the choroid over the ciliary processes. The central layer contains radiate and annular muscle-fibers which find their origin and support in the ciliary body. In this fibromuscular area are cavernous lymph-spaces for the entrance and exit of the aqueous humor which is produced by the ciliary processes. The aqueous humor, a fluid occupying the spaces in front of the lens, is a modified lymph without leukocytic content, containing a very low percentage of protein and sugar. The last is in greater amount than in the blood-serum, and varies directly as this latter, except in diabetes, when the sugar content is relatively very high. The choroid is the posterior extension of the ciliary body and extends to the opening for the optic nerve. The anterior part is supplied with blood by the ciliary branches of the vessels supplying the ocular muscles, the posterior part by the vessels in the optic nerve, and these two sets anastomose.

The Retina.—This layer of the eye is the specialized end-organ of the optic nerve. It spreads from the nerve-head to the ciliary body. It consists from the choroid inward of a pigmented layer upon which lies the neuro-epithelial layer of rods, cones, and fibers, which latter is separated from the nuclear, ganglion, and nerve-fiber layer by a dense neurofibrillar layer. The retina is limited internally by a condensation of nerve-fibers arising in the deeper layers.

The eye lies in the anterior part of the orbit supported by fat and muscles.

CONGENITAL ABNORMALITIES

Anophthalmia is complete absence of the eye, a rare condition; while *microphthalmia*, abnormal smallness of one or both eyes, is more common. Abnormalities due to formations *in defectu* comprise: *synophthalmia*, or *cyclopia*, a condition in which the prosencephalon fails to divide correctly, a single orbit and eye resulting; *cryptophthalmia*, in which the bulb is hidden by failure of the lids to divide. The lids show as the most frequent abnormalities: *coloboma*, an angular defect with its base on the free margin; *congenital ptosis*, and *epicanthus*, a fold of skin passing across the inner canthus from the upper to the lower lid.

THE CONJUNCTIVA

Circulatory Disturbances.—**Anemia** of the conjunctiva alone is an unusual condition, but pallor is common in general anemia.

Hyperemia is common, and has as its chief cause external mechanical irritation, foreign bodies, or gases. It may be a sign of errors of refraction, depending upon physical changes in the eye. It is present as an early stage of inflammation.

Hemorrhage beneath the membrane may occur from traumatism, or by undue muscular effort in the presence of diseased vessel walls.

Edema occurs as part of general edema, or as a result of local venous obstruction, and in infections of neighboring sinuses.

Degenerations of the conjunctiva are rare, but homogeneous metamorphoses have occurred in edematous hyperplastic lesions of the epithelial, areolar, and adenoid layers, to which the names colloid and hyaline or even amyloid degeneration have been given.

Inflammations.—Conjunctivitis may be primary or secondary; the latter arising by extension, or occasionally by infection via the bloodstream. Prolonged irritation by mechanical or chemical agents may occasion a true inflammation, but to these factors is almost invariably added the action of bacteria, of which many different forms have been noted. The principal ones are Morax-Axenfeld's organism, Koch-Weeks' bacillus, gonococcus, pneumococcus, diphtheria and pseudodiphtheria bacillus, *Micrococcus catarrhalis*, streptococcus, *Bacterium xerosis*, and *Bacillus coli*. The pathological changes are congestion and edema of the subepithelial layer, followed by hyperplasia of the adenoid tissue and infiltration. The epithelium is swollen, softened, becomes opaque and desquamates, leaving erosions or ulcerations. The process may be catarrhal, or exudative—serous, purulent, or pseudomembranous. There are several special forms of inflammation hypertrophic in character, such as trachoma, which may be classified as subacute or chronic.

Acute Catarrhal Conjunctivitis.—In this condition there is swelling, redness, and a profuse thin discharge, arising to some extent from the diseased membrane, but chiefly from the overproduction of tears. The redness is greater at or near the canthi. The process may go over into acute purulent conjunctivitis, in which the discharge is purulent almost from its inception. The gonococcus is the commonest cause of the frank purulent conjunctivitis, particularly in the newborn. The conjunctiva and lids in this case are much swollen, and hemorrhages may occur, and there is a profuse yellow or greenish discharge. This form of inflammation frequently spreads to the cornea or uveal tract.

Pseudomembranous conjunctivitis is usually due to the diphtheria organism, but may be caused by other germs. There is much infiltration and induration of the subepithelial tissues, and upon the surface a patchy or continuous membrane may form, beneath which ulcers arise.

Special Forms.—**Spring catarrh, or vernal conjunctivitis,** is a chronic recurring hypertrophic inflammation of unknown cause, characterized by the production of rather flat excrescences upon a smooth, hard conjunctiva. The appearance of the surface is as if a thin film of milk were spread upon it, a condition said to be due to hyalinization below the epithelium. The excrescences are made up of hyperplastic epithelium and connective tissue, the latter being quite homogeneous or

hyaline; in this overgrowth eosinophiles are common. Ulcerations seldom appear in this disease. The secretion is tenacious, yellowish, and may be very profuse.

Follicular conjunctivitis is a subacute or chronic, slightly communicable hypertrophic inflammation characterized by hyperplasia of lymphatic tissue producing elevated granules or follicles, usually following the course of the conjunctival folds. This seldom leads to any cicatrization, although there is a sort of capsule about the lymph-follicles.

Trachoma is a chronic communicable hypertrophic conjunctivitis characterized by the production of papillary granulations, connective tissue overgrowth, and cicatrization, with signs of mild exudative inflammation. These growths appear chiefly upon the lid and at the fornix, and contain the so-called "trachoma bodies," nodules of hyperplastic lymphatic tissue surrounded by a fibrous and vascular capsule.



Fig. 446.—Trachoma, showing round, opaque bodies in upper and lower lids. "Sago-grain" type. From a photograph. Frequent type seen in children (Henry T. Brooks).

The marginal zones of the "bodies" are small and lymphoid, while in the center there are large lymphoid cells with granular nuclei, and frequently the trachoma "cell inclusion," a hyaline body with a bit of chromatic material in it. By some these are said to be like diplococci. Most observers now put them among Prowaczek's Chlamydozoa, while some place them among the Protozoa. Many doubt their etiological relation, as they have been seen in gonorrheal conjunctivitis. Influenza bacilli or closely associated species have been found in trachoma. At all events, the cause of the disease is not yet known, and most observers believe that the infective agent belongs to the filterable viruses. Attempts at cultivation resulted in the development of minute bodies of indefinite morphology. The virus is present in the tears, and seems infective at any time in the course of the disease. It is infective for monkeys. Exposure to a temperature of

56° C. for thirty minutes or to drying for one hour destroys the virus.

The "trachoma bodies" undergo cicatrization and involve the whole lid, and sometimes the bulbar layer, even to the production of entropion in the former, or pannus (granulation tissue) in the cornea.

Pannus is a hyperplastic vascularizing growth of the surface of the cornea due to superficial ulcerative processes. The chief causes are trachoma and phlyctenular disease. The lesion proceeds from the limbus inward, lying between the epithelium and Bowman's membrane, and consisting of cellular infiltration and capillaries, the former preceding the latter. When Bowman's membrane is destroyed the corneal matrix is infiltrated and opacity results.

Parinaud's conjunctivitis is a severe condition with considerable swelling and papillary granulations on the tarsal layer, associated with signs and symptoms of general infection. The disease has been ascribed to a leptothrix, to be found in areas of necrosis in the sub-

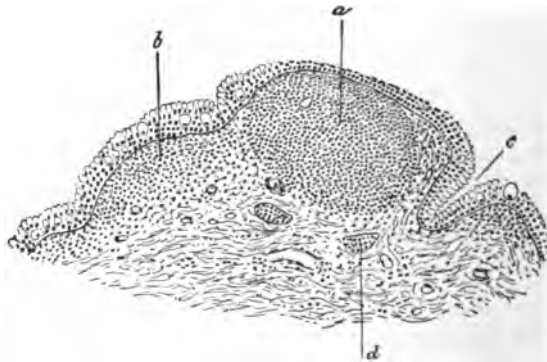


Fig. 447.—Trachoma of the retrotarsal fold: *a*, Follicle; *b*, diffuse infiltration; *c*, Henle's gland with goblet-cells; *d*, lymph-vessel filled with leukocytes; $\times 30$ (Holden).

epithelial tissues. An enlargement of the preauricular glands occurs so often in this condition that it acquires a diagnostic significance.

"Pink-eye" is an acute catarrhal and mucous conjunctivitis due to the Koch-Weeks' bacillus.

Angular conjunctivitis is a contagious condition due to the diplo-bacillus of Morax and Axenfeld, characterized by scanty discharge, congestion of the caruncle, and, microscopically, by epithelial multiplication and desquamation on the tarsal side, with ingrowth thereof at the edge of the cornea.

Phlyctenular conjunctivitis is now believed to be an atypical tuberculous process, and is commonly found in association with tuberculosis elsewhere. It is also frequently associated with eczema. There are small papules or pustules, formed by the accumulation of lymphocytes under the epithelium, which may become pustular, or break down to become ulcers. The condition is commonest on the bulbar layer, and the cornea is frequently involved.

Xerosis is a condition of chronic atrophic inflammation and cicatrization of the bulbar conjunctiva. The two layers may be bound together, and there is frequently a dry scaly membrane on the free surfaces. It is said to be due to the *Bacterium xerosis*, but this is by no means accepted by all ophthalmologists.

Tuberculosis is usually secondary to tuberculosis in the vicinity, but may be primary, as a miliary tubercle or small ulcer. Occasionally caseous masses occur, or a hypertrophic lesion like lupus may arise.

Syphilis.—Characteristic lesions of all three stages have been seen in the conjunctiva.

Pinguecula.—This is a pale yellow triangular chronic thickening of the conjunctiva at the margin of the cornea. This is not a mass of fat, but a proliferation of yellow elastic tissue, and a hyaline degeneration of this and fibrous tissue.

Pterygium is a hypertrophy



Fig. 448.—Phlyctenular conjunctivitis (Children's Hospital) (de Schweinitz).



Fig. 449.—Symblepharon, the sequel of purulent conjunctivitis (from a patient in the Philadelphia Hospital) (de Schweinitz).

of the conjunctiva in triangular shape, proceeding from the palpebral fissure toward the center of the cornea. It is probably due to continued local irritation. Destruction of Bowman's membrane and opacity of the cornea results. The fold is made up of epithelia, beneath which are lymphoid cells and new blood-vessels.

Symblepharon is the adhesion between the bulbar and tarsal conjunctiva due to continued irritation or chronic inflammation. It is a frequent sequel of burns.

Tumors.—Fibromata, papillomata, and lipomata are among the common benign growths, and teratomata have been seen. Angiomata are common in early life, and may be either simple nævi or of a sarcomatous nature. Sarcomata are not common, but develop from pigmented spots at the edge of the cornea. They are exceedingly vascular. The most interesting one is the alveolar sarcoma, or endothelioma, which some observers consider epithelial in nature. Epithelioma is the commonest tumor in this locality, and is a rapidly growing squamous cell growth. Carcinoma may arise from the caruncle.

Cysts may be lymphangiectatic, or as the results of obstruction to glands. Occasionally cysts arise by invagination of epithelium in the

submucous tissue by reason of inflammation or injury. Such folded-in cells continue to secrete fluid and cause cystomata. Cysticercus and filarial cysts have been observed.

LACHRYMAL ORGANS

The lachrymal sac may be the seat of acute inflammation (*dacryocystitis*) by extension through the ducts, by injury, or rarely, primarily. Inflammation, either acute or chronic, may obstruct the flow of tears and distend the sac. Chronic inflammation around the canthus is usually associated with inflammation of the nasal duct and obstruction of tears. Inflammation of the nasal duct may be an extension process from the nose. Occlusion of the duct is temporary in acute inflammations, but stenosis may occur as the result of long-standing nasal disease. *Dacryo-adenitis*, or inflammation of the lachrymal gland, is of any form, and arises from injury or by extension from the conjunctiva upward along the canaliculi.

CORNEA

Keratitis, or inflammation of the cornea, is usually primary, but is occasionally secondary to conjunctival conditions. It assumes two forms, ulcerative or superficial, and non-ulcerative or interstitial. The latter always causes opacity, varying directly according to the severity of the infiltration. Ulceration always results in scar formation, as do the higher grades of infiltration. Milder grades of the latter may be removed without leaving any serious visual defect.

The microscopical changes in keratitis are swelling and degeneration of the corneal corpuscles, about which there may be some proliferation of these cells and an infiltration of a few leukocytes. At the margin of the cornea there is always vascular injection and very early appearance of new capillaries growing in the direction of the lesion.

Infiltration may go on to suppuration and perforation. When ulcerations or suppurations perforate, there is an escape of aqueous and release of pressure with forward dislocation of the iris or even of the lens. The iris may adhere to the edges of the rupture (anterior synechia), and the contact of the lens with the lesion in the cornea may cause anterior polar cataract. Perforation of an infected corneal lesion may lead to pus in the anterior chamber, *hypopyon*. Healing of deep corneal defects occurs by fibrous tissue, leaving opacities. In healing the cornea sometimes is flattened instead of having its normal curvature, a facet being formed; again, a protrusion may occur where the newly formed tissue is not able to resist the intra-ocular pressure—*staphyloma*. Keratitis may lead to panophthalmitis.

Interstitial Keratitis.—This condition, commonly due to general diseases like syphilis and gout, is characterized by the formation of opaque mottlings, or a complete ground-glass appearance of the cornea. It is caused by a cellular infiltrate without tendency to abscess formation. One variety, the marginal, is densest around the scleral insertion,

and, another form, the vascular, shows a production of new blood-vessels (pannus) growing in from the periphery. The epithelium may be eroded or hypertrophic.

Bullous keratitis is a condition in which crops of vesicles appear associated with considerable pain. Herpes of the cornea is of the same nature, but the vesicles are smaller and the cornea may be anesthetic; one variety is due to a disease of the fifth cranial nerve. Another condition associated with the disease of this nerve, with its consequent loss of sensibility of the cornea, is the so-called neuroparalytic keratitis, an ulcerative process limited to the cornea and prone to suppuration.

Ulcerative keratitis may be secondary, or arise as the result of infiltration in the cornea itself. The ulcers may be single or multiple.

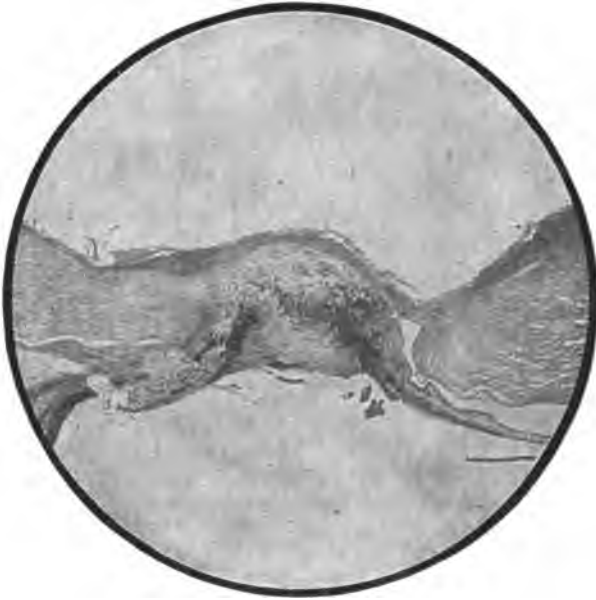


Fig. 450.—Perforating ulcer of the cornea with incarceration of iris (from a photomicrograph) (de Schweinitz).

In the simpler varieties there is a swelling, then denudation of the epithelium, shortly followed by a shallow ragged loss of substance of the cornea. There is only a pericorneal congestion and little tendency to pannus.

Phlyctenular keratitis, associated with the similar disease of the conjunctiva, is characterized by the production of papules composed of lymphoid cells, which tend to soften and form ulcers which spread toward the corneal center, surrounded and followed by new blood-vessels. They heal from the margin, but opacity always results. Perforation or extension by continuity may occur. In healing of superficial ulcers of the eye epithelium grows out to cover the defect before the subjacent tissues heal.

Suppurative keratitis may be diffuse or localized. In either case ulceration with perforation is likely to occur. Serpiginous ulcer, due frequently to the pneumococcus, is perhaps the most common variety. The ulcer spreads superficially rather than in depth, but perforation is not uncommon. Discrete abscesses may occur in the cornea.

Keratomalacia is an acute degenerative (fatty) change of the corneal epithelium, usually associated with inflammation, occurring in debilitated children. Sluggish ulcers may arise.

Ring abscess, or ulcer of the cornea, is merely peculiar in its circumferential spread. The whole cornea may slough off.

Syphilis may appear as an acute or subacute infiltrative lesion, and gumma is known in this locality.

Tuberculosis is usually secondary to adjacent tuberculosis, and appears as an infiltrative and sclerosing process.

Leprosy appears as a nodular keratoconjunctivitis with a histology comparable to that of leprosy of the skin.

Arcus senilis is a hyaline degeneration of the cornea in annular form near the periphery, but separated clearly from the sclera. It usually begins above and extends laterally. It is a pale gray band at first, but later becomes opaque, silvery, or gray white. It is said to be due to faulty nutrition when the circumferential vessels are diseased.

Wounds of the cornea may be superficial, leading to simple destruction of tissue, which is repaired without scar or followed by ulceration and opacities; or penetrating, in which case deeper structures are usually involved and the humors are infected or may escape. Wounds leading to ulceration if associated with extensive fibrous tissue repair may lead to pterygium or, rarely, to symblepharon.

Tumors are exceedingly rare in the cornea. Papilloma and myofibroma have been reported.

Cysts arise in the cornea under the same conditions as in the conjunctiva.

The Anterior Chamber.—Inflammation of Descemet's membrane may arise by extension from inflammation of contiguous structures and presents the changes observed in other serous membranes. Pus (hypopyon) arises in the anterior chamber from any sort of infected corneal ulcer, wound, etc.

SCLERA

Episcleritis is an acute superficial hypertrophic and infiltrative inflammation of the exposed part of the sclera, characterized by low dark red granulations or papules, consisting of lymphoid and polynuclear cells and accompanied by small hemorrhages and edema. This heals without cicatrization. The conjunctiva is movable over these excrescences and is injected.

Scleritis is a deep, diffuse, infiltrative, overproductive inflammation of the sclera, usually of the exposed part, arising, after exposure, in rheumatic, gouty, and syphilitic individuals. It assumes a nodular form associated with hemorrhage and edema. Healing occurs by cicatriza-

tion which leads to thinning and weakening, in consequence of which scleral staphyloma results. One syphilitic form grows as a pericorneal band, consisting, microscopically, of young granulation tissue.

The importance of *injury* to the sclera depends upon whether or not a puncture has been effected with disturbance of relation of the various intra-ocular structures, and the introduction of germs. In the presence of these unfavorable factors healing will take place by scar tissue of course, and lead to destruction of the ciliary body or lens and to weakness of the ball membranes. Tension by scar tissue upon the ciliary body may cause increased intra-ocular pressure. The sclera may be ruptured by a blow upon the eye.

Tuberculosis, syphilis, tumors, and cysts are exceedingly rare in the sclera.

THE CRYSTALLINE LENS

Congenital abnormalities of the lens take the forms of cataract, false position, or abnormal curvature, or it may be involved in a coloboma. Opacity of the lens (cataract) is the principal acquired pathological change. This is due to hyperplasia of the capsular epithelium or degeneration of the internal fibers. When due to the former it is called capsular, when to the latter, lenticular, cataract.

Capsular cataract is usually encountered near the middle of the anterior surface, and is ascribed to some form of insult from the front of the eye, in response to which the lens capsule proliferates, the epithelium first becoming reduplicated, then stratified. An opaque degeneration of the epithelial fibers accompanies or follows the capsular change. Posterior capsular cataract is either congenital, due to the remains of the hyaloid artery, or secondary, due to long-standing disease of the posterior segment of the eyeball, especially in the choroid.

Lenticular cataract is a degeneration involving in part or wholly the fibrillar structure of the lens, rendering it opaque. The traumatic variety is understood, but those due to constitutional disease, inflammations in contiguous structures, or senility are vague in etiology. It is said that the essential feature in all cataracts is an altered tension in the capsule and nucleus, which permits invasion of the fibrous structure by the aqueous humor. The first change seems to be a shrinking of the lens, shortly followed by swelling as the fluid penetrates. This fluid collects in globular masses as do also the remains of degenerated fibers. The capsule may be in natural condition or proliferating. The interior of the lens may soften to a liquid mass in which the nucleus may float or sink (Morgagnian cataract). After the lens has softened some shrinking is noticeable, due probably to beginning absorption.

There are various forms of cataract recognized by ophthalmologists, depending upon the arrangement of the opaque areas. Their pathology is essentially the same however.

A cataract of the lens fiber may arise from any trauma which so affects the capsule as to permit the invasion of the aqueous. It may be a part of or accompanying an inflammation of contiguous tissues.

Dislocation, or luxation, of the lens may occur from trauma or from disease. In the former case the lens may penetrate the vitreous or anterior chamber, or, by rupture of the iris and of the insertion of the cornea, to a position under the conjunctiva. Pathological luxation may be due to degeneration of its suspensory ligament, or in atrophy after cataract.

THE VITREOUS HUMOR

Hemorrhage into the vitreous arises only from injury or disease of surrounding tissues. In the latter it may arise from simple inflammation, but more often it is the result of dyscrasia or diseased vessel walls.

Chemical changes in the vitreous are due to disease of the choroid or retina. They comprise infiltrates of phosphates, fat, cholesterol, or osseous matter. The last supervenes sometimes upon overgrowth of connective tissue from chronic retinitis or choroiditis. Opacities usually arise as a result of these chemical changes. Degenerative changes take the form of fibrillation and liquefaction. The mass soon shrinks by loss of fluid.

Inflammation is secondary to disease in retina, choroid, and ciliary body. Microscopically, there is mild leukocytic infiltration with coarse fibrillation.

The vitreous may escape in punctured wounds, permitting hemorrhage and detachment of the retina. Foreign bodies, filaria, and cysticercus cysts have been found in the vitreous.

THE IRIS

Congenital abnormalities of the iris take many forms, affecting its continuity or pigmentation. Affections of the continuity embrace obstruction of the pupil by persistence of the anterior vascular capsule of the lens which occupies the pupillary space in the embryo; *dyscoria*, irregularity of the pupil and distortion of the iris muscles; *polycoria*, the existence of several openings in the iris; *corectopia*, or incorrect position and shape of the pupil; and *coloboma*, taking the form of a linear defect extending from the pupil even to the ciliary body. Occasionally the coloboma may be very extensive or the iris absent entirely. This is *aniridia*.

Abnormalities of pigmentation consist of its absence, *albinism*; or excess, *melanosis*; or of mixtures of colors, especially eyes of different colors, known as *heterochromia*.

Atrophy of the iris occurs as the result of recurrent acute attacks of inflammation, or by interference with its blood-supply, as from prolonged intra-ocular pressure or traction upon the ciliary body. It may occur as a result of senility. The pathological changes embrace fibrous and hyaline deposits particularly in and around the blood walls, irregularity or loss of pigment, and at times a hypertrophy of the endothelium reflected from Descemet's membrane, a sort of replacement hyperplasia.

Hyperemia of the uveal tract may be an early stage of inflammation, or the result of disease in adjacent tissues.

Anemia is merely a part of general anemia.

Inflammations of the iris may be acute or chronic, but are always exudative in character. The acute may be serous, purulent, simple plastic, or combinations of these.

In **serous** iritis the membrane is swollen, congested, and there is a watery exudate in the anterior chamber which may or may not contain shreds of lymph. This condition is prone to spread to the ciliary body and choroid, thence to the vitreous, which may develop opacities.

In **plastic** iritis, the more frequent form, and usually associated with inflammation in the rest of the uveal tract, the process is of greater intensity, fibrinous exudate appears, and tabs of lymph are found upon the iris and Descemet's membrane; synechia may be found. Synechia may attach the iris to the anterior surface of the lens around the pupillary opening (annular synechia), or the whole iris may become fast (total posterior synechia). The exudate is at times extensive enough to span the pupil. Under these conditions of synechia and closure of the pupil the iris becomes fixed, and outflow of the aqueous humor from the ciliary processes and posterior chamber through the pupil into the anterior chamber is hindered. Then increased intra-ocular pressure arises. This inflammation practically always involves also the rest of the uveal tract.

Purulent iritis may succeed upon the foregoing, and in its spread and results differs little from it except that it is more rapid and extensive. Pus in the anterior chamber (hypopyon) is an almost constant feature.

The pathogenesis of these forms of iritis is essentially the same. The process begins as a congestion and infiltration, usually in the loose layer of the iris, causing hyperplasia or rupture of the endothelium, with a collection of exudate upon this surface that may extend backward to the ciliary body and choroid. There is injection of the pericorneal zone. The causes of iritis, aside from mutilating injury with infection, syphilis, rheumatism, and gout, are obscure. These three last usually cause subacute plastic iritis. Iritis when chronic is commonly syphilitic, and is characterized by endo- and peri-arteritis and accumulations of round and epithelioid cells, the infiltrate frequently showing hyaline change.

Tuberculosis of the iris is probably always secondary, and appears as a diffuse seroplastic thickening, as miliary tubercles, or as a large caseous mass. The miliary form appears as disseminated yellow dots which soon coalesce and extend to the ciliary body. Caseous tuberculosis takes the form of a rapidly growing tumor-like mass composed of fused tubercles, which tends to grow outward and rupture the eyeball. Tuberculosis of the iris is usually unilateral. It is a disease of youth.

Syphilis of the iris appears as a secondary or tertiary manifestation in the form of an acute seroplastic inflammation, or as gumma. The former consists of specific arteritis and peri-arteritis with added round-

cell infiltration. Gummata are commonly found on the pupillary or ciliary borders and do not differ from gummata elsewhere.

Tumors.—Primary tumors are exceedingly rare, melanosis being the principal variety. Occasionally angiomas are seen in the form of *nævi*, which may be pigmented and give rise to sarcoma. It is said that endo- and perithelioma may arise from them.

Cysts.—Parasitic and dermoid cysts have been reported. Sometimes cysts arise from bits of epithelium which have been forced into the iris by violence, as is the case with the cornea.

THE CILIARY BODY

Atrophy of the ciliary body is secondary to inflammation, and occurs in old age. The processes become flattened and the secretory functions disturbed.

Inflammation, or cyclitis, is seldom a solitary process, usually being a part of or secondary to iritis, as iridocyclitis. The process is commonly plastic, although it may be purulent. The condition affects the substance of the body and the exposed part within the posterior chamber. The organization of the fibrinous exudate causes the anterior



Fig. 451.—Traumatic iridocyclitis. Diffuse infiltration of the iris and ciliary body (de Schweinitz).

walls of the posterior chamber to adhere to the lens (*synechia*), and the inflammatory process invades the lens capsule and vitreous. In severe cases the last-named structures are infiltrated, degenerated, and contain opacities. The lens may be dislocated and the uveal tract drawn inward from the sclera by traction of fibrous tissue. The retina may

be detached. These lesions cause such disturbance of nutrition that the bulb begins to soften and *phthisis bulbi* results.

Tuberculosis assumes the same forms as in the iris.

Syphilis of the ciliary body alone is rare, but gummata are reported.

Tumors.—Glioma is the commonest tumor and arises from the retinal segment of the ciliary body. Sarcoma, either simple or melanotic, sometimes occurs.

Cysts are very common, and are said to be due to epithelial inclusions.

THE CHOROID

Hemorrhage in the choroid is common because of the high vascularity of the membrane. Minute hemorrhages occur under various conditions, but their exact cause is not known. They may lead to atrophy of the membrane. Large hemorrhage is due to trauma.

Atrophy of the choroid may be due to hemorrhage, inflammation, or nutritional disturbances. Sometimes collections of so-called "colloid" matter are found among the elastic fibers.

Wounds and ruptures are serious because they usually cause separation of the retina and escape of the vitreous to a position beneath the sclera. The choroid may be detached from the sclera by hemorrhage or exudation.

Inflammation.—In considering inflammation of the choroid it is difficult to separate this membrane from the ciliary body and iris in front, and the retina within. Disease arising in any one of these parts may extend to the others (uveitis), and when all these contiguous structures are invaded the chances of full repair are small. The bulb and its surrounding tissues are swollen and infiltrated.

Choroiditis is an exudative process, serous, plastic, or suppurative in type. Its causes, aside from involvement by extension, are auto-intoxication, gout, rheumatism, syphilis, tuberculosis, and, occasionally, the acute infections, like erysipelas or typhoid fever. It is commonly associated with inflammation of the retina, although one coat may be affected without the other.

Serous choroiditis appears suddenly, with swelling of the membrane and opacity of the vitreous.

Purulent choroiditis follows the same course, but the exudate as a cloudy mass soon infiltrates the ciliary body and iris, and collects in the anterior chamber. The vitreous and retina are shortly involved.

Chronic choroiditis may be diffuse or disseminated. The disseminated forms occasion rounded irregular patches of infiltration over the fundus which spread and coalesce; the retina over them becomes hazy. These infiltrations may dissolve, leaving in their place pale areas of fibrosis which soon take up pigment. These areas may spread by degeneration and connective-tissue growth even after the active inflammation has ceased. They may have calcareous deposits in them. Retinal atrophy over them may result.

Diffuse choroiditis is characterized by the appearance of large yellow

coalescing plaques of exudate over which the retina is edematous. Atrophy of vessels and retinal elements, even of the optic nerve, results.

In acute and chronic cases of choroiditis contiguous structures are usually involved. After choroiditis, especially of recurrent nature, the internal surface tends to form granulation tissue with exuberant growth into the vitreous, with, first, hypertrophy, then atrophy, of the retina. The type of infiltrating cell in both acute and chronic inflammation, except, of course, the suppurative, is that of the lymphocyte series.

Tuberculosis of the choroid is commonly of the miliary variety, but a diffuse infiltrative or large caseous tuberculosis is reported. Miliary lesions seem to occur mostly on the outer surface, while the infiltrative or caseous processes prefer the inner layers.

Syphilis usually causes a serous or plastic choroiditis, but the choroid is seldom involved without the retina.

Tumors.—Sarcoma is the most important, and is usually of the melanotic variety, a very malignant growth giving many metastases. Among the varieties met with there may be melanotic, simple, alveolar, or angiosarcoma, and, related to the last, peri- and endothelioma.

Carcinoma occurs only as a secondary growth, as does glioma.

THE RETINA

Anemia is due to general anemia or obstruction of the central retinal artery by thrombosis or sclerosis. Fatty degeneration may follow it. Blindness results at once from any sudden stoppage of the artery, such as from embolism or spasm.

Active hyperemia is due to long-continued irritation, inflammation, or high arterial tension.

Passive hyperemia is due to: (a) conditions in the eye itself, glaucoma, choked disk; (b) conditions in the orbit, cellulitis, tumors; and (c) conditions away from the eye, heart disease, cranial growth, sinus thrombosis. Grossly, there is lengthening, distention, and tortuosity of the arteries and veins of the eye-ground. Hemorrhage from such vessels may occur.

Hemorrhage.—Retinal hemorrhage occurs from hyperemia, trauma, and vascular disease; in the last are included thrombosis, angiosclerosis, and acute angiitis. The diseases in which hemorrhage is apt to occur are nephritis, diabetes, gout, rheumatism, general arteriosclerosis, anemia, leukemia, purpura, acute infections, and certain poisonings. The hemorrhages appear as radiating red splotches in the neurofibrillar layer, or they may take the form of irregular extravasations into or beneath the retina, or even into the vitreous. The blood may be absorbed and leave areas which undergo fatty degeneration, spots of blood-pigment remaining. Larger hemorrhages may leave an organized clot.

Atrophy is a consequence of prolonged inflammation leading to disturbance of nutrition, or is a senile change. A similar change in the

choroid is usually found. The microscopical alteration consists in a shrinkage of the cellular layer with separation of the rods and cones. The cells and fibers show some fatty metamorphosis, and fibrous tissue increases, particularly between the retina and choroid. Pigment is decreased.

Detachment of the retina is the separation of the membrane by splitting between the pigmented layer and that of rods and cones. It is a serious progressive condition due to some disease or injury to the eye. The membrane remains uncertainly suspended in the vitreous chamber.

Inflammation.—As is the case in inflammation elsewhere in the inner eye, retinitis is infiltrative and exudative. The simplest form is little more than a marked edema of the retina, but deserves to be placed among the inflammations because there may be cellular infiltration associated with edema. This exudate may undergo some form of regeneration. Serous retinitis may proceed to

Purulent retinitis, a condition usually due to perforating wounds, but which also arises metastatically. The process is a swelling with infiltration of pus throughout the retina, which is soon detached, and then the vitreous and anterior segment of the eye are attacked. Hemorrhage frequently occurs. Panophthalmitis always supervenes.

Albuminuric retinitis, a characteristic change in nephritis, is really a neuroretinitis. There is swelling, reddening, and obscurity of the nerve-head, around which spot are radiating linear hemorrhages and pale anemic coalescing areas, which are hyaline or fatty degenerations. The vessels are distended and tortuous. The minute changes are those of chronic retinitis and marked sclerosis of the vessels. Degeneration of the nerve-fibers also occurs.

Diabetic retinitis is a hemorrhagic process. The optic nerve-head is less apt to be swollen, and the retina in general is more normal in appearance than in the preceding, save for irregular or linear hemorrhages. There is, nevertheless, a mild chronic retinitis.

Chronic retinitis assumes many forms for the clinician, but the histological changes are essentially the same in all. There is cellular infiltration of the vitreous layers with fibrous tissue growth inward from the parts near the choroid. In the infiltrate are endothelial cells of obscure origin, probably from the adventitia of blood-vessels, which tissue is actively hyperplastic. Giant cells are common. In the organization of chronic retinitis the choroid may become adherent and the inner retinal fibrillary layers become wrinkled and proliferative, even to the extent of showing granulation tissue. The fibrous layer of the retina may also undergo liquefaction or fatty degeneration. In diffuse retinitis these changes are more or less evenly distributed, but there is a disseminated form in which patches of chronic inflammation occur, and in this variety the internal overgrowth of tissue is commonest.

Retinitis pigmentosa, or **pigmentary degeneration of the retina**, is a chronic progressive atrophic process beginning at the equator or anterior thereto and proceeding backward, characterized by the deposit

of black pigment in splotches with extensive radiations. The retina about the optic disk is the last part to be affected. Under the microscope there is found obliterating endarteritis with hyaline degeneration and deposit of pigment in the vessel walls, and disappearance of the normal pigment.



Fig. 452.—Glioma of retina (patient in the University Hospital) (de Schweinitz).

Tuberculosis of the retina is usually secondary to adjacent tuberculosis. It is of the miliary variety.

Syphilis of the retina in an acute or chronic form assumes the vascular proliferative character peculiar to this infection.

Tumors.—Glioma is the only primary tumor certainly arising in the retina. It is commonly met with in children, and may be due to congenital defect. It is a progressive tumor usually growing forward through the eyeball and presenting a sloughing cauliflower-like mass externally. This tumor is prone to give metastasis to bones and glands; is very cellular and rich in blood-vessels; and most often originates from the inner nuclear layer of the retina.

Angiomata and fibromata are reported, but their origin is not certain.

SYMPATHETIC OPHTHALMITIS

When an eye has been injured, with the result that a uveitis arises, the other and uninjured eye may be affected in sympathy. This sympathetic ophthalmitis takes the form of a subacute remitting or recurrent plastic or serofibrinous uveitis, upon which a panophthalmitis may supervene. Posterior synechia, corneal opacity, staphyloma, or glaucoma may ensue. Sympathetic ophthalmia may follow perforating wounds in the ciliary region, especially if a foreign body be retained; old retinitis with calcification acting as a foreign body; long-standing iridocyclitis; luxation of lens; pressure of an artificial eye; or irritation of the optic nerve stump by fibrous tissue after enucleation. The definite cause is not known, but is variously ascribed to some special micro-organism and reflex nerve irritation. It has lately been suggested that there is very commonly an underlying taint of syphilis or tuberculosis, a proposition strengthened by the beneficial effects, in some cases, of measures directed against these diseases.

GLAUCOMA

The normal intra-ocular tension is maintained by the proper secretion and escape of the aqueous humor. If its escape be hindered, pressure rises and glaucoma results. The condition may be considered primary when no demonstrable cause exists, and secondary when traumatic or inflammatory disease of the bulb has preceded it. The

secondary form is due to synechiæ obstructing the aqueous current between the posterior and anterior chambers, to inflammatory lesions of the ciliary body, or to obstruction at the iridocorneal juncture, including the spaces of Fontana or Schlemm's canal. Such lesions either render the aqueous humor too viscid to filter easily or hinder absorption. Primary glaucoma may arise in the apparently healthy eye. Arterial disease seems to favor its development. The eye in acute glaucoma is swollen, cloudy, injected, lusterless, and the pupil shows a green appear-



Fig. 453.—Section of optic nerve-head containing a deep glaucomatous excavation, the so-called kettle-shaped excavation: *r*, Retina; *ch*, choroid; *s*, sclera; *c*, cup or excavation, pushing back lamina cribrosa (de Schweinitz).

ance. Hemorrhages sometimes occur. In chronic glaucoma there is progressively increasing hardness of the eye, atrophy of the retina, and "cupping of the disk," a condition due to posterior staphylomatous protrusion at the lamina cribrosa with degeneration of the optic nerve.

THE OPTIC NERVE

Hyperemia is found under the conditions given for Hyperemia of the Retina.

Inflammation.—Inflammations affect either the retinal portion of the nerve (papillitis) or the extra- or retrobulbar portions. The causes of this disease are metastatic in infections, or involvement by continuity from the retina, meninges, or orbital tissue. There is also a congestive form in cases of vascular obstruction, such as by intracranial new growths or increase in the quantity and pressure of the cerebrospinal fluid; in this case there is simple edema and hyperemia.

Papillitis, papillo-edema, or choked disk, is a swelling of the retinal end of the optic nerve with indistinctness of its outlines. There may be small hemorrhages, sometimes in radial linear arrangement. The

nerve-head is turbid when infiltration is marked, and minute examination reveals edema, round-cell infiltration, and granular degeneration of the nerve-fibers. In inflammation of the trunk of the nerve infiltration is the same, but one finds proliferation of the endothelial lining of the intraneural spaces and degeneration and atrophy of the nerve-fibers. The form of papillitis dependent upon increased intracranial pressure partakes chiefly of the nature of atrophy, although both this and the atrophies of the *nerve-head* which accompany constitutional disease usually pass through a low inflammatory process similar to that just given. Atrophy of the *optic nerve* from conditions not arising within the eyeball may be due to pressure by lesions in the orbital

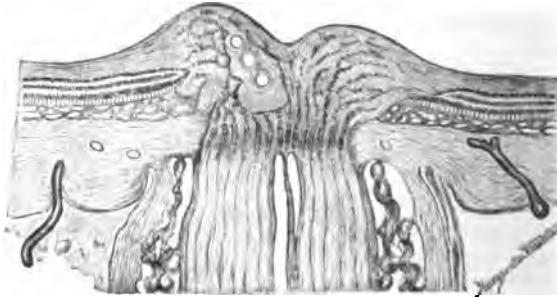
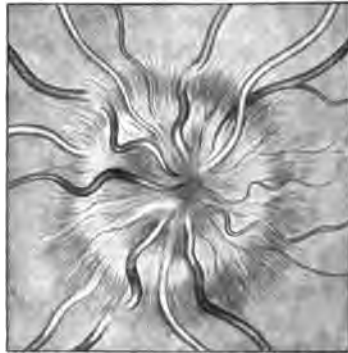


Fig. 454.—Ophthalmoscopical picture of papillitis and semidiagrammatical representation of a longitudinal section of the nerve-head (de Schweinitz).

tissues, or from diseases like paresis and tabes, and poisoning from quinin or tobacco. The degenerations and atrophies depend upon the production of areas of ischemia and upon selective action of poisons for certain nerve elements.

Tuberculosis affects the optic nerve as miliary tubercles in the sheath.

Syphilis takes the form of gumma or neuritis.

Tumors.—The primary tumors of the nerve are divided into the intra- and extradural forms. The former comprise myxoma, fibroma, psammoma, endothelioma, and sarcoma. Extradural tumors are fibroma, endothelioma, and sarcoma.

THE ORBIT

Abnormalities of Position of the Bulb.—The most important condition under this heading is exophthalmos or proptosis. This is due to swelling of the areolar supporting tissue within the orbit, as from inflammation, venous congestion, hemorrhage, or tumors. The results are stretching of the muscles and consequent incorrect position of the eye in the visual axis; stretching of the optic nerve if the protrusion of the ball is greater than the slight amount of slack that the curve in the nerve can give, upon which optic neuritis may ensue. If the lids be unable to close there may arise conjunctivitis and keratitis with ulceration due to the dryness and lack of protection from dust. In exophthalmic goiter the proptosis is variously ascribed to a spasm of the muscle of Müller, orbital hyperemia, and irritation of the sympathetics. In postorbital aneurysmal varices there may be a pulsating proptosis.

Enophthalmos is sinking in of the bulb when the posterior orbital tissues are absorbed, or from a fracture of the skull involving the orbit.

Inflammations affect the orbital tissue as cellulitis or abscess, and arise from injury, extension, or metastasis. Periostitis of the orbital bones may arise under the usual causes for this disease.

Tumors arise from the optic nerve, as above; from the periosteum, fibromata, exostoses, and chloroma; from the ball-supporting tissue, angioma, lymphoma, and sarcoma, including endothelioma. Epithelioma may arise in the lids.

THE LIDS

Edema may be traumatic or accompany ocular inflammation. It occurs in angioneurotic edema and exophthalmic goiter.

Ptosis is incomplete elevation of the upper lid, and may be due to congenital absence of muscle power, or to muscle impairment by palsies of the third cranial nerve.

Inflammation.—Blepharitis, inflammation of the lids, may be a simple catarrhal process, but the more chronic cases assume the form of a productive conjunctivitis and dermatitis. By organization and fibrosis in severe cases the ciliary margin is destroyed and the tear puncta either obstructed or rendered useless by thickening or eversion of the lid. A chronic conjunctivitis and keratitis may ensue.

Stye, or hordeolum, is a small abscess in a hair-follicle. A chronic granuloma of the Meibomian glands with histology like a tubercle, but not of tuberculous nature, is called **chalazion**.

Tumors.—Epithelioma, carcinoma, and, occasionally, sarcoma have been seen. Of the benign tumors, papilloma, fibroma, and adenoma are reported. The glandular tumors arise from sebaceous and Meibomian glands.

CHAPTER XVI

THE EAR

ANATOMY

THE external ear consists of the auricle and external auditory canal. The former is composed of skin and yellow elastic cartilage. The canal is cartilaginous in the outer part, lies within the temporal bone for the inner part, and is lined with skin containing sudoriferous and sebaceous glands which secrete cerumen.

The tympanic membrane separates the external and middle ears. Externally, this curtain is covered by skin, internally, by a mucous membrane between which layers there is a fibrous layer into which the malleus is inserted. At the superior portion of the tympanic membrane there is an umbrella-shaped section of thinner tissue, Shrapnell's membrane, supported on either side by strong fibrous folds. Within the

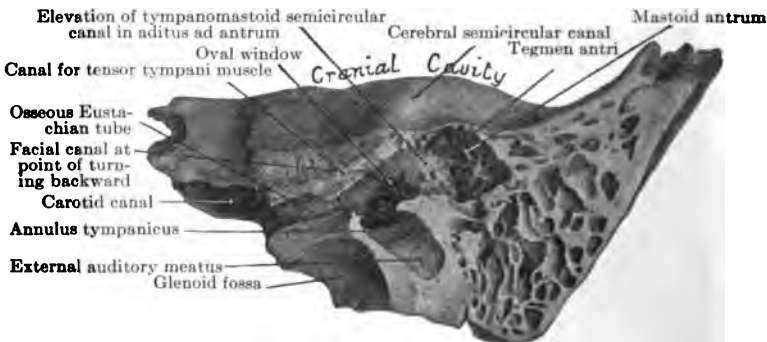


Fig. 455.—Section of temporal bone in plane of mastoid antrum. Aditus, tympanum, and Eustachian tube, showing direct connection of all these spaces (Barnhill and Wales).

membrane, situated in the petrous portion of the temporal bone, is the tympanum, or middle ear. Behind it lies the mastoid portion of the temporal bone with the cells of which there is a communication; below it is the roof of the jugular fossa. From the anterior part of the floor of the tympanum the Eustachian tube passes downward, forward, and inward to the pharynx, through the canalis musculotubularis, which also carries the tensor tympani muscle. There is a natural isthmus of the tube 2.5 cm. from the pharyngeal ostium. The Eustachian tube is lined by ciliated epithelium. Suspended in the tympanum, the chain of ossicles is inserted externally into the external tympanic membrane, internally into the oval window. The cavity is lined by cuboidal epithelium. The internal ear consists of a vestibule

into which the oval window opens, semicircular canals, and cochlea; this is also called the labyrinth, and consists of a membranous part lying in a bony cavity of the same shape and arrangement. The semicircular canals are disposed in the three geometric planes, and the lining is mucous membrane rich in branches of the auditory nerve and covered with ciliated epithelium. The cochlea, a conical spiral body, lies before the vestibule and contains the organ of Corti, the special end-organ of hearing. The auditory, or eighth cranial nerve, passes into the ear by the internal auditory meatus and divides into branches which go to the cochlea, vestibulum, and semicircular canals.

CONGENITAL DEFECTS

The defects in formation of the ear are of little pathological importance, aside from absence or atresia of the meatus, absence of the external tympanic membrane or Eustachian tube, and hypoplasia of the functional structures like the ossicles and internal ear. Whole sections are sometimes missing.

THE EXTERNAL EAR

Hyperemia and **hemorrhage** are of slight importance, and are due to inflammation or injury.

Hematoma auris occurs as a diffuse hemorrhagic extravasation between the cartilage and its covering, and is due to trauma or certain dyscrasias. It occurs frequently in the insane, commonly on the left side, a fact which suggests that trauma may be its cause. Fibrosis, or degeneration of the cartilage, may result.

Deposits of *uratic* or *calcium* salts are sometimes seen in the cartilage or its covering. Within the auditory canal one frequently sees collections of cerumen and desquamated epithelium, even to the extent of forming hard tenacious masses. This is of little importance unless of long standing, under which conditions the skin may show dermatitic changes, and that portion over the drum may become eroded. Foreign bodies are frequently found in the external auditory canal. They may cause inflammation, but are more important because of the reflex nervous phenomena they occasion. Flies may lay their eggs and maggots grow within the canal.

Inflammations.—**Perichondritis** is an exudative process in which the perichondrium is lifted from the cartilage. It may be localized or diffuse. Degenerations of the cartilage may ensue.

Purulent auriculitis may follow the last, but is more apt to assume the form of boil or abscess, beginning in a sweat or sebaceous gland.

The more diffuse non-purulent inflammations of the outer ear usually assume the form of a dermatitis of the canal, which may be of simple infiltrative or pseudomembranous nature. Suppurative processes do occur, but usually after trauma.

Frost-bite of the auricle presents an edematous or bloody swelling which may proceed to ulceration or gangrene.

Tuberculosis occurs as nodular fibrous tubercles without tendency to coalesce, but they do ulcerate late in the disease.

Syphilis occurs as primary lesions, secondary ulcerations in the canal, or gummata.

Mycosis.—Moulds of the genera *Aspergillus*, *Mucor*, *Oidium*, and others grow in the external canal when moisture and a mild dermatitis make favorable soil for their development. The growth may be superficial, or may penetrate the skin or even to the middle ear.

THE TYMPANIC MEMBRANE

Hemorrhage occurs through traumatism, or spontaneously in certain general infections, or in hemophilia, scurvy, and purpura.

Atrophy is the result of long-continued irritation by cerumen, concretions, inflammation, or by increased intra-aural tension by morbid collections. The whole membrane or only its fibrous layer is affected.



Fig. 456.—Normal drum membrane as viewed through a speculum by reflected light (Barnhill and Wales).



Fig. 457.—Bulging drum-head with beginning necrosis at the point of greatest pressure (Barnhill and Wales).

Rupture occurs by direct or indirect injury. Those due to indirect force, blows, explosions, etc., are usually in the anterior or superior parts. The drum may be perforated from within outward by inflammation in the tympanum, or by pressure necrosis; in the first case the membrane itself may be involved. Healing is accomplished by cicatrization, in which the fibrous layer may not be replaced and in which calcification not infrequently appears.

Inflammation.—Acute inflammation is either an infiltrative or catarrhal condition. The membrane is swollen, opaque, and may show small dots of greater accumulation of the exudate. It is due to extension from other inflammations or direct injury.

Chronic inflammation is secondary to acute, or to prolonged or repeated otitis media. There is diffuse or irregular fibrous thickening and nodular granulation tissue.

Tuberculosis occurs as miliary lesions or caseous masses.

Syphilis takes the form of mucous patches or gummata.

TUMORS OF THE EXTERNAL EAR

Polypi are the commonest masses in this situation, and are usually due to overgrowth after inflammation. Various degenerations occur in them. Warts have been seen in the canal or on the drum-head. *Exochondroses* or *exostoses* grow from the perichondrium or periosteum, and may

be sessile or pedunculated. A curious and not uncommon form is annular; it often follows prolonged inflammation and is said to be due at times to too frequent cold bathing.

True neoplasms of this area embrace fibroma, osteoma, chondroma, sarcoma, and carcinoma. Various angiomas are known.

Upon the inner surface of the tympanic membrane cholesteatoma has been found.

Sebaceous and dermoid cysts occur along the canal.

THE MIDDLE EAR

Hemorrhage is due to acute inflammation, trauma, caries of bone involving vascular channels, and it may occur spontaneously in nephritis.

Passive hyperemia occurs in heart and lung disease, or pressure upon the jugular vein.

Inflammation, or Otitis Media.—This disease process appears in acute and chronic types, and assumes a catarrhal, purulent, or fibrosing form. The etiology must consider the three ways in which the tym-

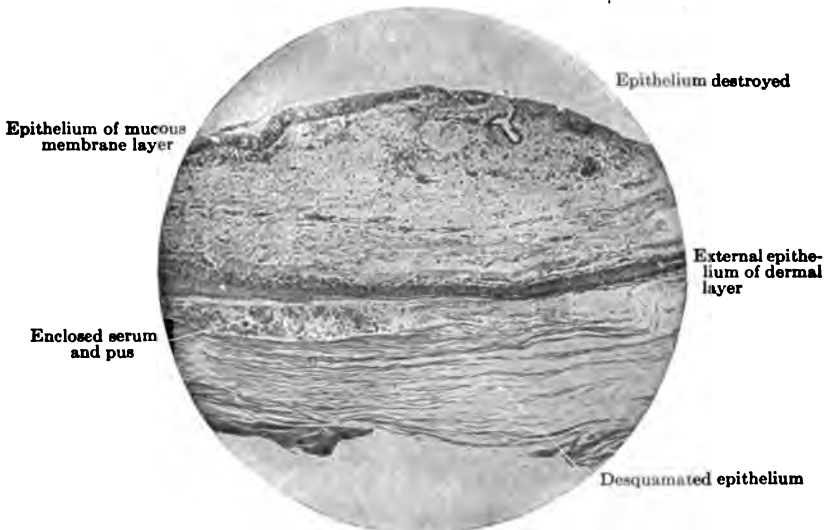


Fig. 458.—Section of drum membrane; case of chronic otitis media suppurativa (prepared by Dr. H. C. Low) (Barnhill and Wales).

panum can be infected. Extension from the pharynx and retro-pharyngeal tissue occurs through the Eustachian tube from various inflammatory foci. Bacteria may be forced up the canal by douching or sneezing. Adenoids favor the collection of microbes near the tube openings in the pharynx (see Eustachian Tube). The cavity may be infected through the tympanum by injury or extension, while in the infectious diseases otitis media may be caused by germs brought in the blood-stream. Staphylococci, streptococci, and pneumococci are the commonest pus formers, but a single kind of organism is seldom present.

Catarrhal otitis media, in its acute form, produces a reddened, swollen, and infiltrated mucosa, and a turbid mucous exudate. The drum is congested and bulges. In the chronic form, either as a successor of the acute, or arising as a result of repeated irritations in rheumatic and gouty subjects, the mucosa is irregularly thickened and may show exuberant fibrous and epithelial granulations. The drum-head is practically always stiffened and the ossicles limited in their movements.

Purulent Otitis Media.—The acute purulent variety is commonly secondary to the catarrhal and there is really no sharp line between the two. The exudate becomes purulent, the infiltrate involves the drum-head, which softens and may slough, and the ossicles loosen or may be necrosed in the severe cases. Extension may take place through the petrosquamosal suture to the meninges or sinuses when the mucosa is ulcerated, or it may burrow to the external surface. The mastoid cells are practically always somewhat involved in otitis media, and when the inflammation is especially severe or protracted necrosis of the mastoid bone and septicemia are apt to occur.

Chronic purulent middle-ear inflammation is a sequel of repeated acute attacks. The mucosa is considerably thickened by round and polynuclear cell infiltration and subepithelial granulation tissue. The cavity is filled with pus and blood, which, when the drainage is poor, may become inspissated. The tympanic membrane is usually perforated and its margins show granulation tissue. The bony casement of the tympanum is attacked by necrosis which may penetrate into the inner ear with extensive necrosis. The ossicles are at first loosened, then become necrotic. The penultimate stage is an enlargement due to the necrosis, while the last phase is one of total necrosis and extension to the skull, meninges, sinuses, or mastoid cells in the unfavorable cases, and fibrosis with bony overgrowth, middle-ear exostoses, in the more favorable ones. The cavity decreases in size in the last instance.

In addition to the above chronic otitides there are varieties of fibrotic change of the soft parts within the tympanum which may be classed as inflammations because they are progressive, although untended with much swelling, congestion, or infiltration. These changes may follow acute inflammation, but may also arise insidiously. One form is the *polypoid proliferative* variety, in which the fungoid masses are covered with cylindrical or ciliated epithelium. *Adhesive otitis* is due to the bridging of the cavity by bands of hyperplastic fibrous tissue. The bands sometimes cut off sections of the cavity, in which fluid collects, the cystic variety. *Sclerotic* otitis is an atrophic variety with interstitial induration, stiffening or ankylosis of the bone chain, periostitis, or exostosis in cases of long duration.

Tuberculosis of the tympanum takes the form of an infiltrative ulcerative caseous lesion which follows the pathological course outlined for chronic purulent otitis media. It is always secondary.

Syphilis appears in the tympanum as an acute or chronic inflammation in the secondary or tertiary stages.

Tumors.—Polypi, the result of inflammation, are the commonest

new growths. They may attain considerable size and protrude externally. They are covered with epithelium which may show any form of metaplasia. Histologically, such masses present angiomatous, myxomatous, fibromatous, or adenomatous characters.

Malignant new growths are uncommon, but sarcoma and carcinoma are the most frequent.

Cholesteatoma.—In some cases of chronic purulent otitis media there arises a mass made up of squamous epithelium and cheesy matter. It is probably the result of metaplasia of the normal columnar epithelium into flat cells, which assume a lamellated arrangement. This so-called cholesteatoma is looked upon by most pathologists as due to prolonged irritation and not as a neoplasm.

THE EUSTACHIAN TUBE

Inflammation, usually of the catarrhal type, is rarely primary, but originates as an extension process from the middle ear or the pharynx. The tube is closed by swelling of its wall and the collection of exudate, thus preventing the passage of air from the pharynx, so that decreased pressure exists in the tympanum from absorption of the air therein. Continued or recurrent inflammations lead to stenosis of the tube, damage to the ear, and deafness.

Obstruction of the Eustachian tube also results from hypertrophic mucous membrane about its opening in the pharynx, or by negative pressure when the nasopharynx is obstructed by adenoids. This decreased pressure draws the mucosa of the tube downward and collapses the lumen at the same time.

THE INTERNAL EAR

Circulatory disturbances of this part of the ear are similar to those given for the tympanum. Hemorrhage is, however, more serious, as it almost always leads to nerve-fiber degeneration, even though quickly absorbed.

In acute infections, leukemia, and pernicious anemia the hemorrhages are small, while in trauma they may be rapidly spreading and destructive. Hemorrhagic extravasation occurs in Ménière's disease, partly, however, of inflammatory origin.

Inflammations in the internal ear are secondary to disease in the middle ear or cranium by extension, or to conditions elsewhere, the blood then bringing the bacteria. The processes are usually acute and follow the pathological changes given for the tympanum, except that to these features must be added alteration of the special sense organs, which easily undergo degeneration and are probably never replaced. Caries and necrosis of the bone frequently occur. When the process is more fibrous one thinks of its probable syphilitic origin. The suppuration in the internal ear spreads to the tympanum or to the skull, to the latter traversing the internal auditory canal along the sheath of the auditory nerve. This is also the course followed in reverse, when meningitic inflammation invades the middle ear.

CHAPTER XVII

THE SKIN

ANATOMY

THE skin consists of two layers: the *epidermis*, composed of stratified epithelium; and the *cutis*, a layer divided into *corium*, or true skin, and the supporting connective tissue below. Some epithelial structures, hair-follicles, sebaceous and sweat-glands, lie in the cutis and subcutaneous tissues. The epidermis consists from without inward of a horny layer of flat translucent cells beneath which is a clear layer of shining cells containing an albuminous substance, eleidin. The next deeper layer is composed of the granular cells of the rete Malpighii, in which lie granules of keratohyalin. Below this are the polygonal cells of the prickle-cell layer lying upon the deepest, or basal cells; these last are ovoid or short cylindrical epithelia. In all the layers of the rete protoplasmic bridges pass from one cell to another. The basal epithelium is the youngest and grows outward to form the upper rows. It rests upon a hyalin basement-membrane, separating the epidermis from the corium. The corium is divided into the papillary and reticular layers. The epithelium follows the curves made by the papillæ of the upper layer. The stalk of the papillæ is made up of delicate elastic and collagen fibers and blood-vessels, while deeper down the connective tissue runs in stout bundles. The subcutis is a looser adipose and connective-tissue layer of quite irregular thickness.

Hair-follicles lie in the corium or subcutis surrounded by a thick fibrous mantle, within which is a hyalin basement-membrane carrying cuboidal epithelium. In the epidermis and to the openings of the sebaceous glands, all layers of epithelium follow the line of the hair-follicle. Sebaceous glands open upon the hair-follicle in the malpighian layer. These glands are racemose in form and the cells correspond to the deep epidermal cells. At the base of the hair-follicle is a papilla of connective tissue upon which rests the group of epithelial cells which form the matrix of the hair.

The sweat-glands are long tubular structures with a coiled internal extremity and a spiral passage through the epidermis.

The blood- and lymph-vessels of the true skin are very numerous and anastomose freely. The nails are stratified layers of horny epithelium arising in a bed made of large papillæ and a wide basal epithelial layer. The *pigment* of the skin lies in the deep layers of the rete of the epidermis and in the corium. It is iron-free melanin, and made by chromatophores in the corium.

It is impossible, within the space allotted to the subject in this book, to give more than the general characters of diseases of the skin. The subject has been greatly studied, but microscopical examination reveals

much less than the clinical observation would warrant one to expect. The skin is in close relationship with some of the internal organs, and is so extensive and in such an exposed position that its lesions are numerous and varied. They are here considered from the standpoint of general pathology, with little reference to the clinical manifestations.

CONGENITAL ABNORMALITIES

Nevus is the most important congenital defect, although not the only one, since whole sections of skin surface may be missing. Nevi appear in the following forms:

Simple angiomatous telangiectasis, wine stain, a flat or slightly raised red or purple stationary growth.

Cavernous angioma, a cystic angioma of blue color.

Pigmented nevi consist of angiomatous, fibrous, and epithelial hyperplasia, carrying pigment both in epithelial and cuticular layers. They may be flat or raised, minute or very extensive, smooth, hairy, or uneven. Microscopically, one finds masses of epithelioid or endothelial cells in the corium about which pigment is deposited.

Sebaceous nevi are flat or slightly raised yellow areas, commonly on hairy parts, the result of increase in the sebaceous glands.

Atypical epithelial growths of surface or glandular cells, congenital in origin, sometimes form raised cystic or solid benign *epithelioma adenoides*. Lymphangiomata of congenital origin sometimes occur in the skin.

ATROPHY, HYPERTROPHY, AND DEGENERATIONS

Atrophy of the skin occurs in senility, as the result of lowered nutrition as in neuritis, after prolonged undue stretching, and, secondarily, in constitutional diseases like diabetes or tuberculosis. The epithelial layer becomes thin, the lower cells are irregularly pigmented, the papillæ are flattened, the hair-follicles shortened, the hairs become wooly or cease to form, the sebaceous glands distend and empty their secretion into the hair-follicles so that both cavities distend to a cyst or *wen*. The collagen or even the elastic fibers of the corium undergo hyalin or granular degeneration. Sweat-glands are usually well preserved.

Hypertrophy of the skin may affect either layer or both, but in any case one layer has more prominent changes than the other. In hypertrophy of the epidermis there is a condition termed hyperkeratosis in which there is reduced desquamation of the horny layer, the cells adhering closely to one another, and the whole layer is firmly applied to the rete, the cells of which may show active proliferation. The commonest epidermal hypertrophy is the *callosity*, due to pressure or rubbing, in which the granular layer of epithelium increases and assumes a dense homogeneous yellow appearance. On the other hand, the rete cells may be pressed down, distort the papillæ and upon them collect into softened masses, or *corns*. *Cutaneous horns*, not infrequently of congenital origin, are due to hyperkeratosis with down-

growth of the basal epithelium into the corium, the papillary layer of which is distorted and may show branching.

Ichthyosis is a congenital or acquired condition characterized by the occurrence of large plates of horny epithelial crust or scales. Under the microscope one finds great widening of the horny layer with plugs of homogeneous epithelial cells filling the outer part of the hair-follicles. There is often excess of pigment in the epithelium lying upon the corium, but the granular epithelial layers may be missing. Not infrequently a mild fibrous thickening of the corium exists, which in congenital or long-standing cases leads to atrophy. In congenital ichthyosis the body is covered with dry folded or scaly skin, traversed by deep fissures, giving the appearance of crocodile skin. In the acquired form the skin is dry, shining, pigmented, and covered with friable crusts or scales separated by cracks.

Warts, or verrucae, are composed of hyperplasias of horny and prickle cells with a slight increase in the corium, while in **condylomata** there are thickenings of both layers. Perhaps the most pronounced part in these formations is taken by the papillary layer, which may grow out like long villi, the surface being covered with very much thickened epithelium. The process is both a hyperplasia and hypertrophy. The connective tissue in both these growths is very rich in blood-vessels. Some leukocytic infiltration appears. Both these hypertrophies are said to be contagious, and this seems surely true of the condylomata, as they are frequently associated with venereal disease and appear most often around the genitals.

The pathology of those conditions affecting the outer layer, or both, having been discussed, it remains to consider the hypertrophies most prominent in the corium. The principal features are increase in the elements natural to the membrane, but to this is added fibrotic changes which naturally follow increase of blood, or succeed upon continued irritation.

Scleroderma is a diffuse or disseminated hypertrophy of the skin of unknown cause, but thought to be associated with nervous or thyroid disease. The skin is hard, firm, and stretched. Under the microscope one finds increase of connective tissue arranged in bands. The skin, muscles, and subcutaneous tissues are involved. The blood-vessels show chronic thickening of all their walls, including obliterating endarteritis. Atrophy soon arrives and leaves a dry, lifeless surface. The epidermis does not suffer. In the congenital forms, called *sclerema*, these lesions are associated with edema, while in the fatty form the corium has a yellow fatty appearance which may or may not be due to true fat.

Elephantiasis is a chronic thickening of the corium and deeper tissues of unknown origin in some cases, while others are due to filaria in the lymph-vessels (tropical form), to passive congestion, chronic dermatitides, like eczema, and to mechanical lymph and blood stasis. The skin is greatly increased in its whole depth, stiff, and cannot be folded, which pachydermatous condition gives the disease its name. Marked disfiguration of legs or other parts is common. The disease

is especially common in the scrotum. Connective tissue increase from the epiderm to the muscles is found by histological study. Elastic fibers are decreased in number. The vessels are fibrosed and thrombotic. Glandular structures soon atrophy.

Necrosis of the skin may be due to injury, or disease of nerves or the spinal cord, and is exemplified in pressure sores (decubitus). There is at first redness and swelling, followed shortly by dense infiltration and dry hardness of the part. Shortly, blisters or blebs form, and the deeper tissues degenerate. An ulcer soon appears with swollen reddened edges, a slough is cast off, and healing occurs by scar formation. The latter part of the process may be considered as *gangrene*. Gangrene of the severer grades, aside from the cases arising from nervous diseases, may follow injury, especially where blood-supply is cut off and cannot be established by collateral means, freezing and burning. In diabetes and ergotism the cause is not clear. In these cases multiple areas of gangrene are common. Senile gangrene of the foot begins in the skin. Some gangrenes, like noma, result from the introduction of masses of bacteria, mostly anaërobic, through wounds.

Symmetrical gangrene of Raynaud is multiple and appears upon corresponding parts of both sides of the body (fingers, ears). It is probably due to combined nerve and vascular defect. Perforating ulcer of the foot is a form of local gangrene depending upon neurotrophic disturbances.

Regeneration of the superficial skin takes place perfectly when the defect has not been deeper than the papillary layer. The rete, from the edges of the defect, grows together until it covers the surface. If, however, the corium has been damaged, scar tissue results, and the defect is replaced by a fibrous tissue poor in vessels and cells. The elastic tissue may be imperfectly replaced, but the glandular structures are missing. If the fibrous tissue be excessive, a prominent hypertrophic scar remains. Atrophic skin is replaced by scar tissue, but traces of the essential tegumentary structures remain.

VARIATIONS IN PIGMENTATIONS

Increase of the pigment affecting a large part of the body occurs in Addison's disease and upon exposed parts after exposure to the sun. Local increase of pigment is found in freckles, in chloasma, or "liver spots." Presence of abnormal pigmentation is seen in jaundice and certain poisonings like that from silver. Increase of pigment may be seen after the absorption of hemorrhagic extravasations.

Decrease of the general pigment is exemplified by *albinism*. Local decrease is seen in *vittiligo* and in scars.

CIRCULATORY DISTURBANCES

Anemia may be general or local. The former is seen in anemia, hemorrhage, and shock. Local anemias are due to cold, vasomotor neuroses like Raynaud's disease, or obstruction to the circulation.

Hyperemia.—Active hyperemia is the result of irritation, excessive warmth or cold, or of internal vasomotor conditions due to toxic or infectious causes. Small local hyperemias are called roseola; general reddening is erythema.

Passive hyperemia, cyanosis, or blue skin, may be general in cases of venous obstruction near the heart, and in circulatory disease due to heart and lung disorders. It is then most marked in the extremities and face. Prolonged pressure hyperemia may lead to edema, or to desquamative, sclerosing, or atrophic dermatitis.

Hemorrhage into the skin takes the form of petechiæ, ecchymoses, vibices (linear), and hematoma. It may occur in the corium alone or find its way to the epidermis. Its characteristic is that it produces a dark red or purple stain that cannot be pressed away. Hemorrhage is

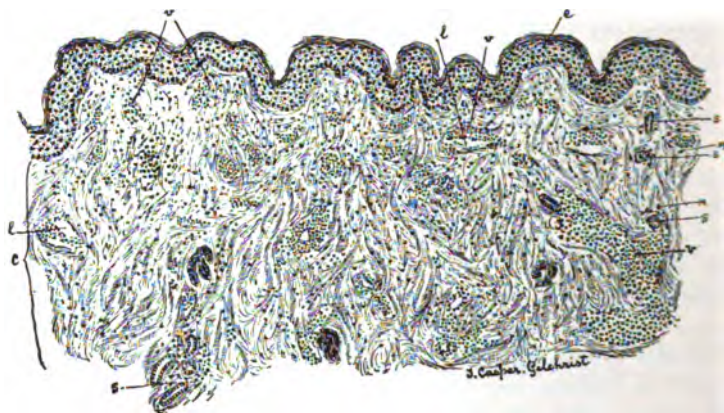


Fig. 459.—Urticaria—section of a wheal: *e*, Epidermis, practically no alteration; *c*, corium, showing acute inflammatory changes, swollen and infiltrated with serous exudation, with the blood-vessels (*v, v, v*), especially those accompanying the sweat-ducts (*s, s, s, s*), dilated and surrounded by and containing numerous polynuclear leukocytes; lymphatic vessels (*l, l*) and spaces also enlarged, containing granular matter; numerous mast-cells (*m, m*) scattered through the corium (courtesy of Dr. T. C. Gilchrist).

met with after some injuries, in infectious diseases, and in the various purpuras.

Edema of the skin is the doughy condition arising when the venous circulation is cut off, the lymph flow obstructed, or the vessel walls and tissue tension changed, as in nephritis. It occurs also in what is called *neuropathic*, *angioneurotic*, or *toxic* edema (Quincke's edema, after eating shell-fish, fruit, etc.), the cause of which is not known. *Urticaria* is a local edema due to irritation or as a part of the last-mentioned group, and takes the form of circumscribed cellular edema of the corium, showing upon the surface as firm, flat, pale elevations with a pink margin (hives, dermatographia).

INFLAMMATION (DERMATITIS)

The inflammations of the skin are exudative in character for the most part, but are accompanied by certain hyperplastic, degenerative,

and desquamative processes in the epidermis which lend to them at times a catarrhal appearance. Changes in one layer without concomitant alterations in the other are rare. Following the plan noted in an earlier paragraph, there will be given here the pathological manifestations in the various layers without dwelling long upon the clinical appearances, the most important objective factor in the study of diseases of the skin at the present day.

The causes of dermatitis are numerous and varied. They embrace injuries of various kinds by heat or cold; chemical and mechanical agents; intoxications by exogenous or endogenous substances; infective vegetable and animal organisms, and they may be the result of altered nutrition from faulty innervation or blood-supply. The cause of many dermatitides has not been discovered.

The evidences of inflammation of the skin fall into certain fairly well-defined classes, and it is perhaps well that the reader be familiar with the terms given to the eruptions and their pathological meaning.

Erythema is diffuse reddening of the skin with or without swelling, and subject to great variations.

Macules are non-elevated, clearly outlined areas, presenting any color known to the skin. The size is usually small.

Papules are elevated areas of various shapes, usually small and with clear margins. A mixture of these last two is known as a maculopapule.

Tubercles are sharply outlined firm swellings larger than papules, and sometimes warty in appearance.

Vesicles are localized collections of clear fluid the size of macules or papules, within the epidermis or between it and the corium.

Bullæ, or blebs, are large vesicles arising by separation of large areas of epidermis from its base by fluid, or by coalescing of vesicles.

Pustules are vesicles containing pus. If very large, they are called **ecthyma**.

Crusts are masses of dried exudate and epithelium.

Scales are sheets of dead epithelium.

The simplest inflammations of the skin, such as are found in scarlatina, in food-poisoning, or in idiopathic erythema, take the form of congestions of the corium, with varying grades of transudate or even cellular exudation. This may be confined to the corium and epidermis, but in the more severe grades, as scarlatina, it penetrates to the subcutis. These conditions are for the most part devoid of exudate upon the skin surface, but are followed at times by scale formation. The inflammation may be diffuse, as in measles or food-poisoning, or localized, as in erythema nodosum.

The next higher grade of inflammation is indicated by more intense edematous and cellular infiltration of the upper layers of the corium, with penetration of the fluid to the malpighian epidermal layer. The fluid pushes aside the cells of the basal and prickle cell layers, where it may form vesicles, being held in place by the horny layer through which the fluid cannot pass. The deep epithelium becomes necrotic and softens,

a process which may be due to the actual cause of the dermatitis in some cases, and is, therefore, primary. The vesicles may dry and cover themselves with a crust, or break and leave a weeping surface. The histological changes in the corium are cellular edematous swelling of the papillary layer, congestion, and perivascular collections of round cells. For examples of this process one can turn at first to *herpes* in any of its various forms. This condition presents patches of small vesicles tightly filled with clear or slightly cloudy fluid, surrounded by an areola of swollen injected skin. The vesicles are situated in the deep layers of the rete. The cause of herpes is not known, but the disease is thought to be

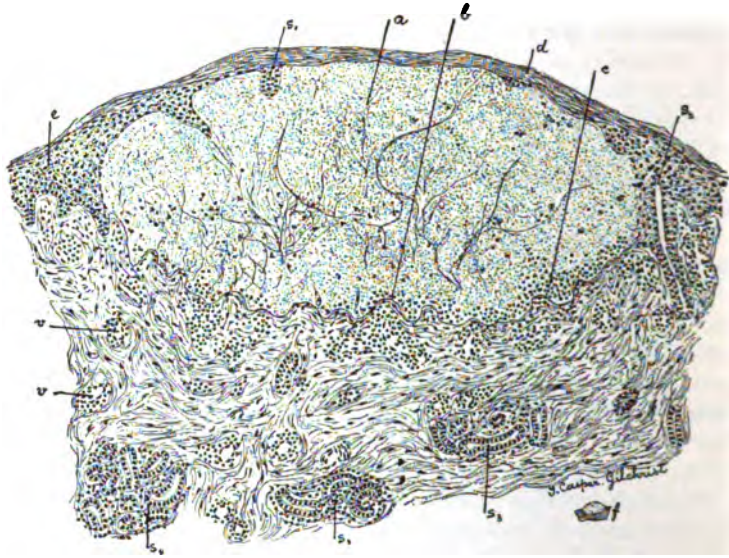


Fig. 460.—Pemphigus—a beginning bleb (a) between corium and the epidermis, the bared papillæ (b) forming the base; acute inflammatory changes in the papillary layer of the corium, with marked serous exudation, particularly about the vessels; reticular part of the corium and the sweat-glands (s_1 , s_2 , s_3 , s_4) are practically normal, except where the sweat-ducts (s_1 , s_2) are involved in the bleb-formation: d, corneous layer; e, rete; v, blood-vessels; c, cell masses at base; f, about the natural size of bleb examined (courtesy of Dr. T. Caspar Gilchrist).

due to nerve irritation or an infectious agent. A more extensive vesicular process is found in *pemphigus*. Here one finds large bullæ upon normal or slightly swollen bases, with clear or slightly cloudy contents. The cysts arise by exudation between the corium and the epidermis, although at times some epithelium is seen lying upon the papillæ. The blebs become purulent, burst, or dry and form crusts. The cause of the various forms of pemphigus is not known, but it frequently appears upon syphilitic newborn children.

Frankly infectious forms of vesicular dermatitis are *varicella*, *variola*, and *impetigo*. The first and the last form their vesicles fairly high in the epithelial layer, while the variola virus causes an early degeneration of the basal cells of the rete malpighii, to which suppuration is

soon added. Impetigo is a disease due to some pyogenic organism; the vesicles are always purulent, and leave crusts upon a granulating surface.

Severe insults to the skin, like *burning*, *freezing*, and concentration of *light rays*, produce an exudative dermatitis with fluid collections in the epidermis. This result is due both to exudation and damage to the epithelium itself. The vesicles, or blebs, are filled with serum, which may escape by rupture of the horny layer, thus leaving a weeping surface. In the severer burns this stage is short, a slough forming very early. In freezing, the same lesions may appear, but gangrene is more apt to occur.

Eczema.—This affection of the skin with its protean manifestations belongs in the exudative class because, with the exceptions of the very destructive or very old cases, the lesions, under the microscope, are

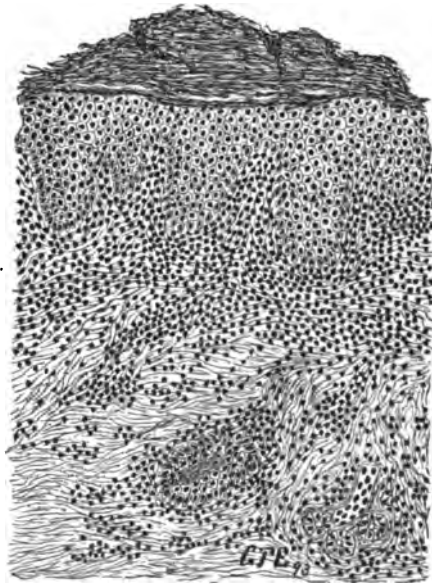


Fig. 461.—Eczema seborrhoicum, section of a small papule in the type commonly known as "seborrhea corporis." A hyperplastic horny layer and dense inflammatory cell-infiltration in more or less of the entire corium, with slight edema (courtesy of Dr. Geo. T. Elliot).

essentially the same as in the immediately preceding groups. Clinically, the disease has innumerable modifications, but it commonly begins as an erythematous or vesicular dermatitis. The infiltration and swelling of the papillary layer are marked, especially about the enlarged blood-vessels and lymph-channels. Vesicles occur in the usual manner by destruction of the deeper epithelium by pressure, but in their absence an excess of fluid is present in the epidermis. This fluid finally finds its way to the surface and the superficial cells are removed in crusts. To replace the lost surface cells the deeper layers actively push out and new super-

ficial layers are formed without the normal keratin (parakeratosis). This leaves a surface covered with cells of the malpighian layer, a softer, pinker, more sensitive, and probably weeping area. In chronic cases, however, especially of the dry varieties, there is a hyperkeratosis, a condition in which the excessively produced epithelial cells are not desquamated, but remain as crusts or scales. The papillæ are variously altered also by fibrosis in chronic cases. The cause of eczema is unknown. It has been ascribed to infection and endogenous or exogenous intoxication.

The consideration given to the imperfect formation of the horny epithelium in eczema leads to a discussion of those inflammations in

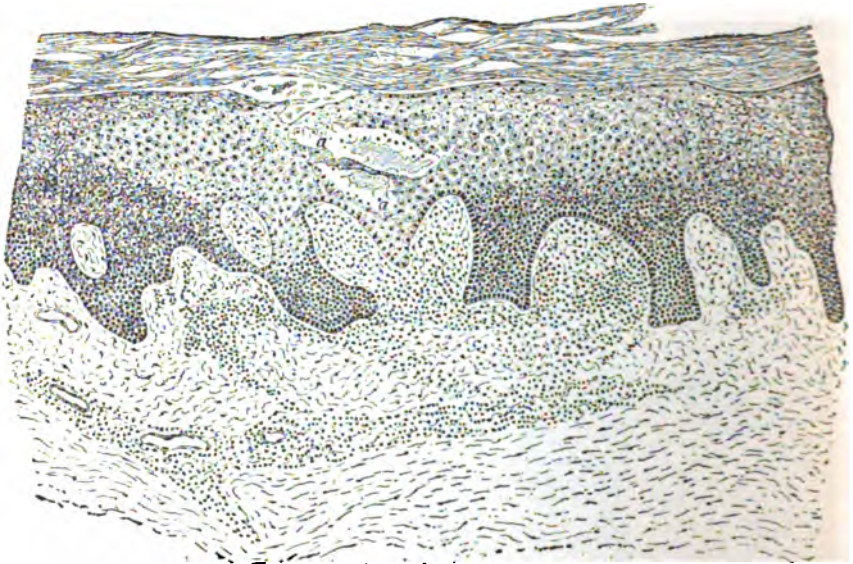


Fig. 462.—Eczema—sluggish, deep-seated, vesicular type, with scattered lesions and somewhat thickened corneous layer, commonly seen on the fingers; section from palmar surface of a finger (low magnification): *a, a*, Represents a vesicle in the earliest observable stage; the mucous layer in the lighter part shows molecular changes, and corresponds to the area of inflammation in the papillary layer of the corium below. The papillæ show marked serous exudation, dilated blood-vessels, and invasion of leukocytes (courtesy of Dr. A. R. Robinson).

which, by reason of faulty nourishment of the epithelium from the corium or functional disarrangement of the deeper layer of the epidermis, an abnormal or excessive production of horny epithelium (para- or hyperkeratosis) takes place and expresses itself in cast-off scales of various dimensions. In those conditions where the frank inflammatory lesions recede, less fluid passes through the rete malpighii, but, nevertheless, a disturbance of this layer exists. It consists in a separation of the cells, degeneration of some of them, and irregular hyperplasia to make up for the cast-off superficial layers. Irregular horny layers are produced and cast off because of the lesions below, which consist of fibrous changes of the papillary layer, or even deeper. In this class fall *psoriasis* and

lupus erythematosus. In *psoriasis* the horny layer is increased in thickness, and the cells separated by leukocytes, organisms, and air, to the last of which the silvery sheen of the crusts is ascribed. The rete cells are separated and hyperplastic and fluid lies between them. Keratohyalin is lacking. Distinct thickening occurs in the corium and the papillæ are irregular.

To this exfoliative class belongs also pityriasis rubra, a condition in which the corium changes are equal in importance to the epithelial, and which goes on to atrophy.

In *lupus erythematosus* the corium shows fibrous thickening and obliterating endarteritis which lead to atrophy and cicatrization. The epithelial layer is thickened, broad scales lying upon the hyperplastic rete.

Papular eruptions are known in many skin diseases. As would be expected, the chief seat of the swelling is in the corium, where a local-

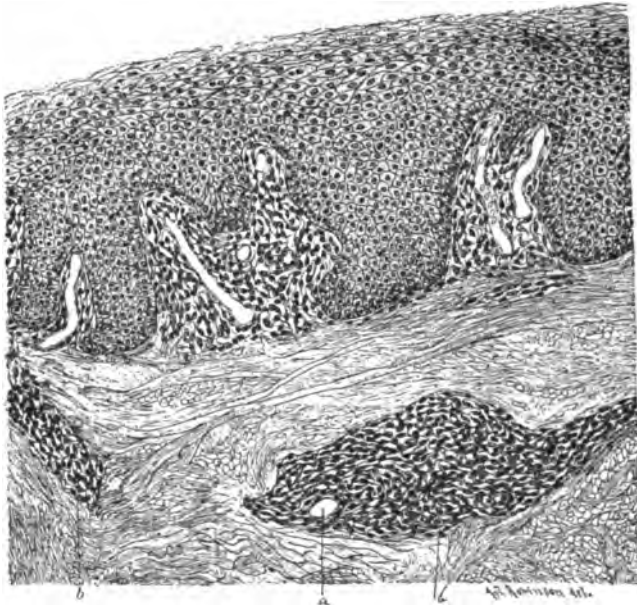


Fig. 463.—Psoriasis—from a chronic patch—showing marked hyperplasia of the rete extending deeply downward as interpapillary prolongations, thus giving the papillæ increased length. The secondary inflammatory changes in the corium are seen, with enlargement of the blood-vessels (a), in the cutis proper as well as the papillæ, and extensive (b, b) perivascular cell-infiltration (courtesy of Dr. A. R. Robinson).

ized cell and fluid infiltrate occurs. To this may be added a hyperplasia of the epithelial layer, the cells of which are separated by fluid or leukocytes. True vesicle formation may occur on top of a papule. In other cases the papule may be caused by an increase in the rete epithelium alone, either on the free surface or at the openings of glands. *Prurigo* and *lichen* belong to this class of pathological changes in pure form, but it should be remembered that papules may occur in almost any dermatitis.

Inflammation Chiefly Affecting Hair-follicles and Sebaceous Glands.—

These two structures are usually involved together by reason of their close anatomical association. An obstruction to the outlet of the follicle dams back secretion, and bacteria, sinking in along the hair, easily invade the gland. Obstruction can take place when accumulations of epithelial cells and sebaceous material become dried about the hair. This may hold back the secretion until it becomes hardened into a comedone. If this retained secretion becomes infected

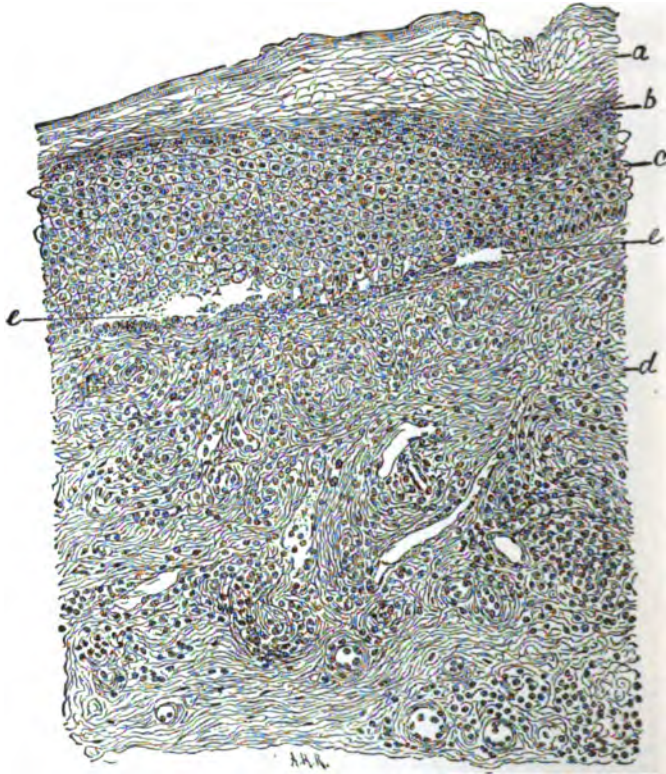


Fig. 464.—Lichen planus—section from a chronic patch (moderately high magnification): *a, b, c*, Show respectively the corneous layer, granular layer, and rete—all considerably thickened; *e, e*, microscopical cavities, with serous exudate; *d*, corium, infiltrated with exuded round cells, and with marked increase in the size of the connective-tissue corpuscles (courtesy of Dr. A. R. Robinson).

by pus cocci, various lesions arise. In some, as **sycosis**, the hair-follicle and its surroundings show the most effect, while in **acne** of the simpler variety the disease is fairly well limited to the sebaceous gland.

Acne vulgaris is an adenitis or folliculitis, expressed by small pustules and a mild concomitant dermatitis, due to bacterial infection. Some persons seem to have a special disposition to it, especially at puberty. It may occur after the use of bromids and iodids. **Sycosis** is probably due to a mould. It is a folliculitis chiefly near the skin surface, but may extend deeply into the sebaceous gland.

Acne rosacea is a diffuse sclerosing dermatitis with increased sebaceous secretion from hypertrophic glands which may or may not show inflammatory changes. It occurs commonly on the nose and cheeks as a red, irregular, uneven, or nodular patch. Vessels are large and distended; fibrous tissue is increased and may constrict the sebaceous gland ducts.

Furuncle is a localized suppuration of the skin starting in a sebaceous gland, and characterized by the formation of a central necrotic slough and a densely infiltrated wall separating it from the healthy tissue. This wall is not sharply defined, but fades into healthy parts. The cavity, after evacuation, heals by granulation. Furuncles are due to the pus cocci penetrating the follicles, especially when favored by slight injury.

Carbuncle is a compound furuncle formation characterized by soft necrotizing spread and multiple sloughing openings in the skin. This

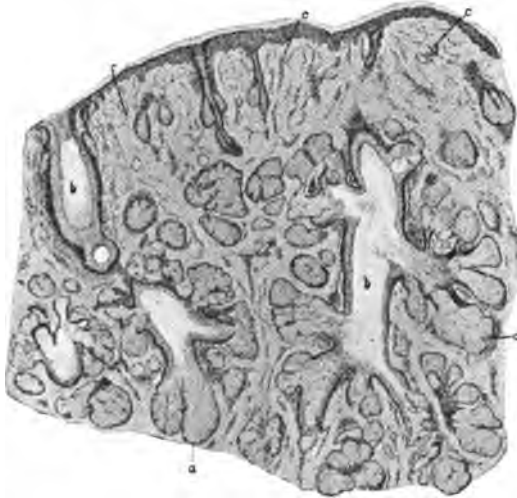


Fig. 465.—Acne rosacea: a, Enlarged sebaceous glands; b, their distended ducts; c, increased vascularization (Aschoff).

is due to staphylococci or streptococci. General lowered vitality favors the inflammation, and furuncles appear as skin complications in diabetes, marasmus, and the like.

Malignant pustule, or anthrax, is a localized suppurative and gangrenous process. There occurs rather superficially a dark red or brown edematous and indurated swelling which soon softens in the center, but underneath there is a firm slough. The minute pictures show a purulent collection containing anthrax bacilli in the deeper epithelial layers, elevating the epidermis from the papillæ. The inflammatory process in these last three conditions is one of fibrinous, purulent, and liquefactive character.

Inflammations Chiefly Affecting the Corium and Subcutis.—Diffuse

inflammations take the form of infiltrations, which range from simple edema with congestion to suppuration. They all tend to spread, but in so doing are preceded by a zone of congestion or dense infiltration. The simplest of these processes is **erysipelas**, an acute or subacute infection due to streptococci. There is congestion and serous or serofibrinous infiltration. **Cellulitis** is next in severity, affecting chiefly the subcutaneous tissue, although the true skin is almost always infiltrated. In this lesion there is extensive fibrinous and cellu-

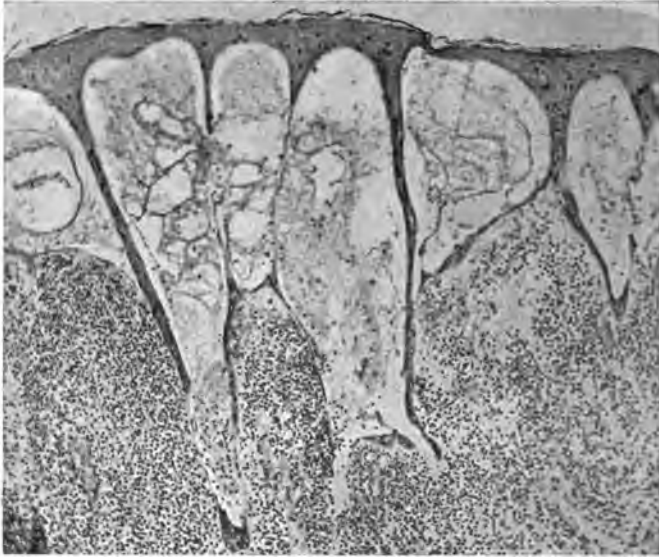


Fig. 466.—Vesicles on surface of pustule due to the anthrax bacillus (Mallory).

lar exudate. It is commonly the result of infection through the lymphatics. **Phlegmon** is the name given to a true suppuration in the corium and subcutis. It is a rapidly spreading purulent infiltration, which may break outward and discharge, or penetrate the muscles inward.

Ulcers of the skin, be they infectious, like soft chancre, or due to metastasis through lymph- or blood-stream, begin by serous or serocellular infiltrate of the deeper epidermis with extension outward and inward. Of course, whole sections may be discharged when phlegmon has isolated an island of skin by cutting off its nutrition.

SPECIFIC INFLAMMATIONS

Under this heading come the class of infectious granulomata and mycotic diseases. The etiology and histopathology of the former have already been discussed (see Chapter V), and it remains to be pointed out here how they appear in the skin.

Tuberculosis of the skin, or *lupus*, may be primary or secondary, in the former case being directly inoculated into wounds. It occurs in

many forms, as flat thickenings, as uneven, slightly raised areas, or as excrescences, or even verrucæ. The tuberculous process assumes the diffuse fibrous form, with here and there giant cells, and an occasional fully formed miliary tubercle. There is little tendency to caseation in the ordinary sense. The seat of the lesion is the corium, the supporting fibers of which layer degenerate. There are numerous lymphocytes and mast cells about the infiltrate. The epidermis is little affected, except in the warty inoculation form, when it may be thickened in the horny layer. Tubercle bacilli are difficult to discover in the lesions of lupus. General fibrosis of the lesion is a common method of healing, and scar tissue is extensive and disfiguring. The common form is known as **lupus vulgaris**, which appears usually upon the face. The primary inoculation, or warty form, is **lupus verrucosa**, seen oftenest upon pathologists, veterinarians, and butchers. Two forms of ulcerative tuberculosis of the skin in early life are the miliary and scrofuloderma, the latter being common near caseous glands, and seeming to be an infiltration with fibrosis and atrophy due to the adjacent lesion.

Syphilis.—The primary lesion, or chancre, occurs usually on the genitals, but may be implanted anywhere. It appears as a hard mass, occupying all layers of the skin, and shows a tendency to early ulceration. The firmness is due to a dense infiltration and proliferation in the whole corium, being diffuse in the papillæ, and close about the blood- and lymph-vessels lower down. Multiplication of connective-tissue cells soon appears. The *Spirochætas* are found everywhere, but especially near the vessels and in their walls.

The secondary lesions may assume any form of eruption known to the skin. They have a tendency to be pigmented and polymorphous. Early in the disease the eruption is symmetrical, but later it is commonly localized. Histologically, there is an infiltrate of small round cells in the papillary layer and increase of connective-tissue cells here and there deeper in the corium. Exudates of fluid character may appear either in the papillary layer or rete malpighii.

Gumma, or the tertiary lesion, appears as a firm swelling, rather deep in the skin, which shows a tendency to soften and ulcerate outward. (See Histology of Gumma.) *Spirochæta pallidæ* are numerous in the secondary lesions, especially those giving a moist surface (condyloma latum), but they are found with difficulty in gummata.

Leprosy.—The lesions of leprosy take place in the corium and subcutaneous tissue, and seem to have a predilection for nerves and their surroundings. They compress glandular structures. Connective tissue overgrowth is common in later stages.

Actinomycosis and glanders occur in the skin by direct inoculation or by extension. The process is one of necrotizing cellulitis surrounded by granulation.

Mycosis fungoides has been described (see page 199).

Mycoses of the skin are caused by moulds (hyphomycetes), which invade the epidermis and the structures arising therefrom, especially

the hair-follicles. Blastomycetes also produce a dermatitis, but penetrate to the corium or are brought thither by the blood or lymph.

Favus is an inflammatory mould disease presenting yellow concave crusts, or *scutula*, which are made up of the mycelium of the moulds and epithelium. These are well fastened to the deep horny layer. The mould may penetrate the hair-follicle, and in the epidermis is found a leukocytic infiltration. The mould is *Achorion schönleini*.

Tinea, or **ringworm**, is a dermatomycosis due to members of the genus *Trichophyton*.

Tinea tonsurans gives a dirty gray crust of mould and epithelium upon hairy parts. The hairs are broken by the growth of mould within and around the hair. The base of the eruption is round and consists of swollen, slightly indurated skin, which may or may not be inflamed.

Tinea circinata is probably a result of the same infection as the last, but occurs in less hairy parts of the skin. It grows in a spreading circular manner by the spread of moulds within the deep epidermal layers. A mild congestion of the corium occurs.

Tinea sycosis, also of trichophyton nature, occurs over shaven beards, and is due to the growth of mould into the hair-follicle and sebaceous gland. It is acneiform in appearance.

Tinea, or **pityriasis versicolor**, is a desquamative condition due to the presence of *Microsporon furfur* in the horny epithelium. There are yellowish, reddish, or brownish spots covered by scales. There is little inflammation.

Erythrasma is a scaly eruption upon warm and moist parts. It is said to be due to a microsporon species.

Blastomycosis and the related **coccidioidal granuloma** (see page 348) are specific inflammations of both the epidermal and dermal layers. The affections present a diffuse thickening of the skin, with warty and ulcerative eruptions similar to epithelioma and tuberculosis. Papules or pustules may form. The lesions in the epiderm are infiltration of polynuclears between the deep epithelial layers, the cells of which are swollen and separated, and hyperplasia with irregular prolongations into the corium. Abscesses form, in which may be found the round or elliptical yeasts. Prickle cells are prominent, a feature which, when combined with the miliary abscesses, is very characteristic. The horny layer is widened and irregular. In the corium are small abscesses containing the organisms, a diffuse granulation tissue with cells of the small lymphoid series, endothelium, and, occasionally, a giant cell.

Dermatitis Due to Animal Organisms.—The most important form is **scabies**, the itch, due to the *Acarus scabiei*, an arthropod. The female burrows a track in the horny epithelium, where she lays her eggs. These hatch out, and the young burrow further. The inflammation that follows is due more to scratching than to the parasites, which, however, have some irritative action. Pediculi (lice) and fleas bite the skin, and produce an irritation. The dermatitis that appears is due to scratching, and may in prolonged cases take the form of a weeping eczema.

Epithelioma or **molluscum contagiosum** is a flat or slightly raised, firm mass supplied with a central depression and opening, having a waxy or pearl-like color, commonly the size of a pea, and situated most often upon genitals and head. By some its contagious character is denied. It consists, under the microscope, of radially arranged hyperplasia of the rete malpighii, separated into lobes by fibrous projections of the corium, which layer is much distorted by this downgrowth. In the center is a mass of desquamated cells and detritus which can be pressed out of the gross lesions. The rete cells are degenerated and

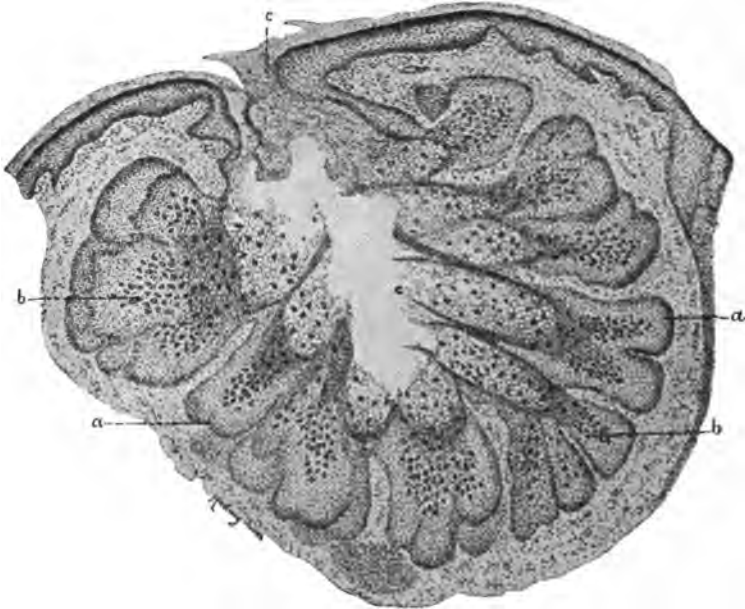


Fig. 467.—Molluscum contagiosum: *a*, Lobular epidermal growth; *b*, molluscum bodies; *c*, detritus as contents of central spaces (Aschoff).

many contain the so-called “molluscum bodies.” These are clear spaces situated near the nucleus, and may at times or by special stains show an amorphous chromatic mass. They are probably degenerative or may be included with the Chlamydozoa.

TUMORS

Fibroma is the commonest benign tumor of the skin. It appears as single large, firm swellings, or as multiple soft growths, sometimes individually, at others in groups, which arise from the connective tissue of nerve-sheaths (neurofibroma). **Keloid** is another fibromatous tumor of the skin.

Lipoma occurs as single large, lax masses, or as multiple small growths, which may be symmetrically distributed. **Xanthoma** is a tumor related to lipoma, appearing as yellow plates or warty masses.

It lies in the corium, and consists of connective tissue surrounding groups of fat-like, refractile bodies (*xanthoma* bodies) and clusters of epithelioid and multinucleated cells, arranged usually near blood-vessels. This tumor occurs in diabetes and occasionally in icterus.

Myoma sometimes occurs in the skin, as do **osteoma** and **chondroma**.

Angioma has been considered under *Nevi*, but those tumors consisting of vessels and proliferated lining membranes, the *endo-* and *peritheliomata*, are occasionally met in the skin. They are related to—

Sarcoma.—This tumor in its pure form is rather rare in the skin, in which it has been known to take any form. By far most frequently the melanotic form is seen. These tumors arise from *nevi* and develop in spindle cell or alveolar form. They contain atypical chromatophores. A special form is the idiopathic multiple pigmented sarcoma of Kaposi, a disseminated variety of granulomatous and angiomatous nature.

Epithelial tumors are the commonest new growths of the skin, and appear as epitheliomata and glandular cancers.

The **squamous epithelioma** appears as a nodular growth, tending to ulcerate early, to spread out, and to be surrounded by a hard raised edge. It grows downward into the deeper tissues with finger-like projections visible to the naked eye. Under the microscope there are numerous pearls in the closely packed epithelial masses. The commonest seats for this growth are where skin and mucous membranes join. Metastasis to the lymph-glands is common.

Rodent ulcer is an epithelioma in which the actively growing tumor cells retain more of the shape and size of the basal cells of the rete malpighii than is the case with the preceding form. The cell masses are in the form of anastomosing columns, and have few or no pearls. Paget's disease of the nipple is of this character.

Carcinoma basocellulare of Krompecher retains throughout the basal cell characters and grows as rounded nests containing central degenerative cysts, or as branching tubular cell projections.

Benign cystic epithelioma is one of the new growths retaining the basal cell characters, said by some to grow from sebaceous cyst ducts, by others from hair-follicles, and by still others from the rete of the surface epidermis.

Lenticular carcinoma, or **cancer en cuirasse**, is that form which tends to spread under the skin, causing dense infiltration. It is usually secondary to cancer of the mamma. Carcinoma of the skin arises from its glands, and is discussed later. Secondary malignant tumors are not common in the skin.

STRUCTURES WITHIN THE SKIN

SEBACEOUS GLANDS

Seborrhea is a hypersecretion of sebaceous matter which may give rise to a scaly *seborrhæa sicca* when a mixture of sebum and epidermal scales dry upon the surface, or *seborrhæa oleosa* if the skin remains

oily; dandruff and smegma in excess are respective examples. If protracted in duration and excessive in degree, a complete dermatitis may arise.

A **osteatosis** is a deficiency of sebum, and is a constant companion of many dermatitides, but is rare as a primary process.

Comedo is the accumulation of inspissated sebum held within the gland by a plug of epithelium, dried sebum, and dirt in the opening of the hair-follicle. The cause is probably a hyperplasia of the super-



Fig. 468.—Comedo, showing distention of duct and slight glandular disintegration (greatly magnified) (courtesy of Dr. T. C. Gilchrist).

ficial gland cells, although it may have a deeper significance, since it is so constant at puberty as to be almost physiological at that time of great activity of the skin. If the hyperplasia be prolonged, acne results.

Wens, or **sebaceous cysts**, may be considered as an exaggeration of the foregoing, the enlarged gland being surrounded by a connective-tissue capsule.

Milium is the appearance of small pale masses, the result of accumulation of sebum in the gland when the duct is completely occluded.

Acne.—(See page 1000.)

Tumors.—Adenomata, simple or of the cystic papillary type, and true carcinomata are known.

SWEAT-GLANDS

Hyperidrosis and **anidrosis** are respectively excessive and deficient or lacking sweat secretion. They may be associated with other disorders, but are obscure in origin otherwise.

Bromidrosis, or malodorous sweat, is usually a peculiarity of an individual or due to some nervous disorder.

Chromidrosis, colored sweat, is due to excretion of something taken into the stomach or to local bacterial infection.

Sudamina is the eruption of tiny vesicles in the epidermis, due to blocking of sweat-gland ducts or their rupture as they pass through this layer.

Inflammation of the sweat-glands is known as **hydradenitis**.

Cysts and adenomata sometimes arise in sweat-glands.

HAIR

Hypertrichosis is excess of hair, and may be congenital or due to irritation.

Alopecia is congenital absence of hair, or its disappearance during life. In the acquired form it may occur without apparent cause as the result of atrophy of the skin, or following acute infection. In the form of **alopecia areata** hair disappears in sharply outlined patches, leaving the skin smooth, flat, and dry. It may spread until all parts are denuded. There is atrophy and slight cellular infiltration of the skin, and the pigment is decreased.

Trichorrhexis is an unusual fragility of the hairs.

Canities.—This name is given to loss of color of the hair in spots. It has as its cause, probably, a nervous disorder. Pigment is lacking and air is found in the shaft.

NAILS

The nails respond to slight injury by the appearance of white spots, probably due to air or small hemorrhages between the epithelial layers. Furrows across the nail occur after acute illness, or in delayed growth from any cause. Inflammation of the matrix (*onychitis*) or its surroundings (*paronychia*) is the result of causes similar to those given for dermatitis. It is commonest in syphilis and tuberculosis. Nails may be ribbed and distorted (*onychogryphosis*), and penetrate the skin at the side, the so-called *unguis incarnatus*, or ingrowing nail. This may lead to inflammation or suppuration.

Various inflammations—syphilis, favus, eczema—may involve the nail-bed.

Tumors.—Fibroma, echondroma, and carcinoma may appear under the nails.

INDEX

ABDOMINAL pregnancy, 805
 Abortion, tubal, 804
 Abrin, poisoning from, 34
 Abscess, 133
 alveolar, 602
 of brain, 913
 of liver, 662
 of lung, 564
 of prostate, 824
 of spleen, 446
 of thyroid gland, 700
 of tonsils, 605
 of vulva, 808
 periappendiceal, 638
 perinephric, 725
 psoas, 869
 retropharyngeal, 603
 Acervuloma, 204
 Acervulus, 715
 Acetonuria, 760
 Achondroplasia, 837
 Achromatic substance, 893
 Acid intoxication, 42
 excessive, 42
 in man, 42
 etiology of, 42
 symptoms of, 43
 Acid-proof bacilli, 324
 Acne, pancreatic, 690
 rosacea, 1001
 vulgaris, 1000
 Acrania, 887
 Acromegaly, 841
 Actinomyces bovis, 341
 cultivation of, 342
 pathogenicity of, 343
 madurae, 346
 Actinomycosis, 148
 definition of, 341
 etiology of, 341-343
 of bones, 853
 of brain, 919
 of heart, 497
 of intestines, 648
 of liver, 672
 of lungs, 580
 of mouth, 600
 of muscles, 869
 of pericardium, 502
 of skin, 1003
 of thyroid, 705
 pathological anatomy of, 345
 physiology of, 346

Addison's disease, 709
 Adenocarcinoma of mammary glands, 835
 Adenofibroma of uterus, 785
 Adenoids, 605
 Adenoma, appearance of, 216
 definition of, 215
 etiology of, 215
 nature of, 219
 of kidney, 744
 of liver, 674
 of mammary glands, 833
 of pituitary body, 714
 of suprarenal bodies, 711
 of testicles, 822
 of thyroid gland, 705
 of uterus, 787
 of vulva, 809
 seats of, 216
 structure of, 216
 Adenomatous goiter, 702
 Adenomyoma of uterus, 785
 Adenosarcoma of testicles, 822
 Adhesions, formation of, 138
 Adipose tissue, regeneration of, 154
 Age in carcinoma, 221
 in disease, 19
 Agglutination, bacterial, 265
 in typhoid fever, 292
 Air-embolism, 64
 Albinism, 974, 993
 Albuminoid degenerations, 85
 Albuminuria, 761
 Albumosuria, 761
 Bence-Jones, 762
 Alexin theory of immunity, 256
 Alkaptonuria, 760
 Alopecia, 1008
 areata, 1008
 α -granules, 417
 Alveolar abscess, 602
 angiosarcoma, 201
 sarcoma, 194
 Amebic dysentery, 640
 Amitosis, 150
 Amnion, 810
 Amyelia, 933
 Amylaceous bodies of prostate, 825
 Amyloid degeneration of muscles, 868
 formations, local, 93
 infiltration, 91
 definition of, 91
 etiology of, 92
 microscopical appearances of, 93

- Amyloid infiltration of heart**, 482
 of kidneys, 739
 of liver, 661
 of lymph-glands, 453
 of mucosa of intestines, 631
 of pancreas, 686
 of pericardium, 504
 of pituitary body, 714
 of spleen, 448
 of stomach, 620
 of suprarenal bodies, 709
 pathological anatomy of, 92
 physiology of, 94
 reactions for, 93
 seats of, 93
Amyloidosis, 91
Anal fissure, 634
Anaphylaxis, 270
Anaphylotoxin theory of infection, Fried-
 berger's, 271
Anatomy, morbid, 17
 pathological, 17
Anemia, 431
 aplastic, 437
 definition of, 431
 hemolytic ictero-, 438
 local, 58
 of brain, 902
 of bronchi, 532
 of conjunctiva, 965
 of esophagus, 609
 of heart-muscle, 481
 of kidneys, 718
 of larynx, 527
 of liver, 654
 of lungs, 538
 of mouth, 594
 of muscles, 863
 of pharynx, 602
 of pia-arachnoid, 874
 of retina, 978
 of skin, 993
 of spinal cord, 937
 of stomach, 613
 progressive pernicious, 435
 splenic, 444, 447
Anemias, classification of, 431
 primary, 433
 secondary, 431
 etiology of, 431
 pathological anatomy of, 432
 physiology of, 433
Anencephaly, 890
Aneurysm, 511
 conditions in other parts associated
 with, 516
 definition of, 511
 dissecting, 515
 ectatic, 513
 etiology of, 512
 false, 517
 miliary, 513
 of arteries of brain, 901
 of heart, 496
 pathological anatomy of, 513
 saccular, 514
Aneurysm, spurious, 517
Angina, herpetic, 603. See also *Pharyn-
 gitis*.
 Ludwig's, 608
 pectoris, 492
 Vincent's, 340, 607
Angioma, 181
 cavernous, 991
 of bones, 853
Angioneurotic edema, 74
Angiosarcoma, 200
 of brain, 921
Angiosclerosis, 507
Anguillula intestinalis, 400
 stercoralis, 400
Anhydremia, 425
Anidrosis, 1007
Animal parasites, diseases from, 364
 in kidneys, 747
 transmission of disease, 410
Aniridia, 974
Anisocytosis, 420
Ankyloglossia, 594
Ankylosis of joints, 855
Ankylostoma duodenale, 397
Anlage, Baumgarten's, 19
Annelides, 405
Anophthalmia, 965
Anteflexion of uterus, 772
Anteversion of uterus, 772
Anthracosis, 100, 562
Anthrax, 1001
 definition of, 308
 etiology of, 308
 mode of infection in, 309
 of intestines, 648
 of muscles, 869
 pathological anatomy of, 310
 physiology of, 310
Antibacterial immunity, 269
Antigens, chemistry of, 272
Antitoxic immunity, 268
Antitoxin, action of, 261
 elimination of, 262
 transmission of, 261
Anuria, 758
Aorta, stenosis and atresia of, 469
Aphthæ, Bednar's, 595
Aphthous stomatitis, 595
Aplasia, 76
Aplastic anemia, 437
Apoplexia serosa, 904
Apoplexy, 907
Appendicitis, interstitial, 637
 obliterating, 638
 pathological anatomy of, 637
 relapsing, 638
 results of, 637
Aqueduct of Sylvius, 884
Arachnitis adhesiva, 930
Arachnoid fluid, 924
Arcus senilis, 972
Argyria, 101
Arsenic, action of, 33
Arterial disorders, 57
Arteries, 503

- Arteries, anatomical considerations of, 503
 congenital defects of, 503
 of brain, aneurysms of, 901
 arteriosclerosis of, 900
 colloid degeneration of, 901
 hyaline degeneration of, 901
 syphilis of, 901
 syphilis of, 511
 tuberculosis of, 511
 Arterio-capillary fibrosis, 507
 Arterioliths, 72
 Arteriosclerosis, 507
 changes in other organs from, 510
 etiology of, 507
 in nephritis, 736
 of arteries of brain, 900
 pathogenesis of, 507
 pathological anatomy of, 508
 results from, 510
 Arteritis, acute, 505
 productive, 505
 suppurative, 505
 obliterating, 505
 proliferating, 505
 Arthritis, acute, 856
 atrophic, 859
 chronic, 856
 purulent, 857
 serous, 857
 deformans, 857
 clinical types of, 858
 etiology of, 859
 nomenclature of, 859
 dry, 859
 gonorrheal, 769
 gouty, 860
 hypertrophic, 859
 neuropathic, 860
 rheumatoid, 859
 Arthropoda, 405
 Ascaris canis, 395
 lumbricoides, 395
 Ascites, 692
 Asphyxia, 28
 Aspiration pneumonia, 554, 557
 Asthma, thymic, 712
 Astrocytes, 920
 Atavism, 21
 Ataxia, Friedreich's, 948
 Atelectasis, 546
 congenital, 546
 in later life, 547
 Atmospheric pressure, decreased, in
 etiology of disease, 28
 increased, in etiology of disease, 27
 Atrophic gastritis, 616
 Atrophy, brown, 77
 definition of, 76
 etiology of, 76
 numerical, 76
 of bone-marrow, 464
 of bones, 847
 of choroid, 977
 of glands of stomach, 620
 of heart, 493
 Atrophy of iris, 974
 of kidneys, 737
 of larynx, 529
 of liver, 657
 acute yellow, 659
 red, 657
 of lungs, 543
 of lymph-glands, 452
 of mammary glands, 830
 of mouth, 598
 of mucosa of intestines, 631
 of muscles, myopathic, 867
 neuropathic, 866
 secondary, 867
 progressive, 866
 pseudohypertrophic, 867
 simple, 867
 of nerves, 959
 of optic nerve, 982
 of pancreas, 685
 of pericardium, 504
 of prostate, 824
 of retina, 978
 of skin, 991
 of spleen, 448
 of testicles, 817
 of tongue and cheeks, 598
 of uterus, 783
 pathological anatomy of, 76
 physiology of, 77
 progressive spinal muscular, 951
 simple, 76
 Auricular septum, defects of, 469
 Auriculitis, purulent, 985
 Auriculoventricular orifices, stenosis and
 atresia of, 469
 Auto-intoxication, 24
 Autolysis in cellular necrosis, 116
 Autonomous new growths, 159
- BACILLARY dysentery, 639
 Bacillus, 243
 aërogenes capsulatus, 312
 coli communis, cultivation of, 296
 distribution of, 296
 morphology of, 296
 pathogenicity of, 296
 pathological physiology of, 297
 synonyms of, 295
 fusiformis, 340
 icteroides, 351
 oedematis maligni, 311
 of Ducrey and Unna, 302
 of dysentery, 297
 proteus, 351
 pyocyaneus, 329
 smegma, 324
 tetani, 306
 tuberculosis, artificial culture of, 315
 avian, 315
 bovine, 315
 demonstration of, 316
 distribution of, 317
 human, 314
 modes of infection in, 317

- Bacillus typhi abdominalis**, 289
Bacteria, action of, 241
 biology of, 245
 chemical conditions of growth, 246
 chemistry of, 245
 chromogenesis of, 251
 classification of, 241
 of diseases from, 37
 diseases due to, 273
 effect of heat on, 246
 of light on, 246
 of toxic products of, 251
 fate of toxins of, 250
 ferments of, 247
 functions of, 247
 higher, diseases due to, 341
 in etiology of disease, 37
 involution forms of, 245
 local effects of, 251
 mechanical conditions of growth, 246
 morphology of, 243
 nature of, 241
 not causing specific infection, 349
 physical conditions of growth, 246
 products of, 247
 in culture-medium, 250
 proteins of, 247
 toxalbumins of, 249
 toxins of, 249
Bacteriaceæ, 242
Bacterial agglutination, 265
 theory of immunity, 259
 immunity, 265
 toxins, poisoning from, 34
Bacteriolysis, bacterial immunity as applied to, 266
Bacteriolytic theory of immunity, 257
Bacterium anthracis, 308
 diphtheriæ, 285
 mucosum capsulatum group, 329
 pestis, 300
 pneumoniæ of Friedländer, 283
 rhinoscleromatis, 304
Bacteriuria, 763
Balanitis, 814
Balantidium coli, 379
Banti's disease, 448
Basophiles, 416
Baumgarten's anlage, 19
Bednar's aphthæ, 595
Beggiatoaceæ, 242
Bence-Jones albumosuria, 762
Beriberi, 359
Bile-ducts, dilatation of, 681
 stenosis of, 680
Biliary cirrhosis, 668
 obstructive, 669
 ducts, inflammation of, 678. See also *Cholangitis*.
Bilirubin in urine, 766
Black tongue, 598
Bladder, calculi in, 755
 results of, 755
 carcinoma of, 758
 changes of position of, 752
 exstrophy, 752
Bladder, fibro-adenoma of, 758
 fibroma of, 758
 foreign bodies in, 755
 hemorrhage of, 753
 hyperemia of, 753
 inflammation of, 753. See also *Cystitis*.
 malformations of, 752
 myoma of, 758
 myxoma of, 758
 papilloma of, 757
 polypoid outgrowths of, 757
 rupture of, 753
 syphilis of, 755
 tuberculosis of, 755
Blastomycosis, 348, 1004
Blebs, 995
Bleeders, 62
Blepharitis, 983
Blood, alterations in, 68
 anatomy of, 412
 changes in, 57
 character of, in leukocytosis, 429
 crises, 421
 diseases of, 412
 disturbances of circulation of, 56
 foreign bodies in, 442
 formation of, 419
 in leukemia, 440
 parasites in, 442
 plasma of, 419
Blood-current, alterations in, 68
Blood-plaques, 419
Blood-platelets, 419
Blood-poisons, poisoning from, 35
Blood-vessel walls, changes in, 68
Bone-marrow, 462
 atrophy of, 464
 chloroma of, 466
 fatty infiltration of, 463
 hypertrophy of, 464
 in leukemia, 464
 inflammation of, 465
 mucoid degeneration of, 464
 myeloma of, 466
 necrosis of, 464
 pigmentation of, 464
 tumors of, 466
Bone-sand, 850
Bones, actinomycosis of, 853
 anatomy of, 836
 angioma of, 853
 atrophy of, 847
 carcinoma of, 854
 caries of, 846
 chloroma of, 854
 chondroma of, 853
 cold abscesses of, 850
 comminuted fracture of, 839
 compound fracture of, 839
 cysts of, 854
 development of, 836
 diseases of, 836
 disorders of development of, 836
 enostoses of, 853
 exostoses of, 853
 fibroma of, 853

- Bones, giant growth of, 841
 - hemorrhage from, 841
 - hyperemia of, 841
 - hypertrophy of, 841
 - hypoplasia of, 847
 - intermediary callus of, 840
 - lepra of, 853
 - lipoma of, 853
 - myelogenous callus of, 840
 - myeloma of, 854
 - myxoma of, 853
 - necrosis of, conditions associated with, 847
 - definition of, 846
 - pathological anatomy of, 846
 - osteoma of, 853
 - parasites of, 854
 - periosteal callus of, 840
 - regeneration of, 153, 839
 - sarcoma of, 853
 - osteoid, 854
 - secondary, 854
 - sequestrum of, 846
 - syphilis of, 851
 - conditions associated with, 853
 - congenital, 852
 - etiology of, 852
 - pathological anatomy of, 852
 - syphilitic gumma of, 852
 - thrombosis of, 841
 - tuberculosis of, 849
 - conditions associated with, 851
 - etiology of, 849
 - pathological anatomy of, 849
 - seats of, 851
 - tuberculous abscesses of, 850
- Bordet-Gengou bacillus of whooping-cough, 299
- Bothriocephalus mansoni, 394
- Bovine tuberculosis, 318
- Bow-legs, 855
- Brain, abnormalities in size of, 888
 - abscess of, 913
 - actinomycosis of, 919
 - anatomy of, 882, 883
 - anemia of, 902
 - angiosarcoma of, 921
 - arteries of, 900. See also *Arteries of brain*.
 - carcinoma of, 922
 - circulatory disturbances of, 902
 - compression of, 918
 - concussion of, 917
 - congenital abnormalities of, 887
 - development of, 882
 - diseases of, 870
 - edema of, 904
 - embolism of, 908
 - fibroma of, 921
 - fissures of, 883
 - ganglionar neuroglioma of, 920
 - glioma of, 919
 - hyperemia of, 903
 - hypertrophy of, 889
 - hypoplasia of, 889
 - lacerated wounds of, 917
 - Brain, lymphangioma of, 921
 - osteoma of, 922
 - partial absence of, 890
 - perithelioma of, 921
 - physiology of, 885
 - postmortem degenerative conditions of, 886
 - psammoma of, 922
 - punctate wounds of, 918
 - red softening of, 909
 - sarcoma of, 920
 - sclerosis of, atrophic, 899
 - diffuse, 899
 - disseminated, 915
 - hypertrophic nodular, 900
 - lobar, 914
 - multiple, 915
 - secondary degeneration after hemorrhage of, 907
 - syphilis of, 919
 - thrombosis of, 908
 - total absence of, 890
 - tuberculosis of, 918
 - tumors of, 919
 - white softening of, 909
 - yellow softening of, 909
 - Brain-sand, 715
 - Bread-and-butter pleurisy, 588
 - Bright's disease, acute, 722
 - Brill's disease, 355
 - Bromidrosis, 1008
 - Bronchi, anatomical considerations of, 531
 - anemia of, 532
 - congenital malformations of, 532
 - dilatation of, 535
 - foreign bodies in, 537
 - hemorrhage of, 532
 - hyperemia of, 532
 - inflammation of, 532
 - obstruction of, 534
 - parasites of, 537
 - stenosis of, 534
 - syphilis of, 536
 - tuberculosis of, 536
 - tumors of, 536
 - ulcers of, 534
 - Bronchiectasis, 535
 - Bronchiolectasis, 536
 - Bronchiolitis, 556
 - exudativa, 534
 - Bronchitis, acute catarrhal, 532
 - chronic catarrhal, 533
 - fibrinous, 533
 - Bronchogenic purulent pneumonia, 563
 - tuberculosis, 567
 - Bronchopneumonia, catarrhal, etiology of, 553
 - pathological anatomy of, 554
 - simple, 554
 - Brown atrophy, 77
 - Bubo, 769
 - Bubonic plague, definition of, 300
 - etiology of, 300
 - pathological anatomy of, 301
 - physiology of, 302

- Bullæ, 995
 Burdach, column of, 884, 932
 Bursæ, inflammation of, 862
 Bursitis, 862
- CACHEXIA strumipriva**, 706
 Caisson disease, 27
 Calcareous infiltration of pericardium, 504
 of pia-arachnoid, 929
 Calcicosis, 100
 Calcification, 96
 definition of, 96
 etiology of, 96
 of choroid plexus, 923
 of kidneys, 739
 of lymph-glands, 453
 of muscles, 868
 of spleen, 449
 of stomach, 620
 of testicles, 817
 of veins, 518
 pathological anatomy of, 96
 physiology of, 98
 seats of, 97
 Calculi in pelvis of kidney, 749
 mulberry, 756
 pancreatic, 690
 Calculus of bladder, 755
 Callosity, 991
 Callus, intermediary, 840
 myelogenous, 840
 periosteal, 840
 Cancer en cuirasse, 835, 1006
 special forms of, 230
 Canities, 1008
 Carbohydrate metabolism, diseases of, 47
 Carbonates in urine, 766
 Carbuncles, 135, 1001
 Carcinoma, age in, 221
 appearance of, 221
 basocellular, 1006
 congenital theory of, 220
 definition of, 219
 degenerative changes in, 225
 dyscrasia in, 221
 etiology of, 219
 glandular, 229
 heredity in, 221
 infectious theory of, 220
 lenticular, of skin, 1006
 nature of, 226
 of bladder, 758
 of bones, 854
 of brain, 922
 of ductless glands, 711
 of Fallopian tubes, 802
 of intestines, 649
 of kidney, 744
 of larynx, 530
 of liver, 675
 of lungs, 581
 of lymphatic glands, 462
 of mammary glands, 833
 of ovaries, 796
- Carcinoma of pancreas, 689, 698
 of penis, 815
 of prostate, 828
 of spinal cord, 957
 of spleen, 449
 of stomach, 623
 pathological physiology of, 625
 varieties of, 624
 of testicles, 822
 of thyroid gland, 705
 of urethra, 770
 of uterus, 788
 of vagina, 807
 of vulva, 809
 pathological physiology of, 226
 seats of, 222
 structure of, 223
 traumatic theory of, 220
 varieties of, 227
 Cardioliths, 72
 Caries of bones, 846
 of teeth, 601
 Cartilage, regeneration of, 153
 Caruncle of vulva, 809
 Caseation, 110
 of testicles, 817
 Casts, blood-, 734
 cellular, 734
 crystalline, 734
 fatty, 735
 granular, 735
 hyaline, 734
 leukocytic, 734
 tube-, 733
 waxy, 734
 Cataract, capsular, 973
 lenticular, 973
 Catarrh, acute nasal, 525
 spring, 966
 Catarrhal bronchopneumonia, 553
 enteritis, 633
 inflammation, 135
 jaundice, 635, 684
 pharyngitis, 602
 stomatitis, 595
 Caustics, action of, 31
 Cavity formation in lungs, 572
 Cecitis, 636
 Cecum, inflammation of, 636
 Cell contents, 243
 division, direct, 150
 epithelioid, 141
 irritation, 416
 multiplication, 150
 plasma, 416
 spider, 885
 stimulation, 416
 Cell-membrane, 244
 Cellular necrosis, alterations in cell
 nuclei in, 114
 in form of cell in, 114
 autolysis in, 116
 circulatory phenomena in, 116
 etiology of, 114
 general pathology of, 114
 karyolysis in, 114

- Cellular necrosis, karyorrhexis in, 114
 - pathological anatomy of, 114
 - postmortem alterations in, 115
 - degeneration of tissues, 116
- Cellulitis, 1002
- Cephalohematoma, 842
 - internal, 870
- Cercomonas coli hominis, 367
 - hominis, 366
- Cerebellum, anatomy of, 884
 - hypoplasia of, 889
- Cerebral hemispheres, hypoplasia of, 889
- Cerebrospinal fluid, 924
 - hypersecretion of, 922
 - in disease, 925
 - meningitis, epidemic, 877
- Cervix, chronic endometritis of, 778
 - hypertrophy of, 783
 - phagedenic ulceration of, 780
 - syphilis of, 782
- Cestodes, 384
- Chalazion, 983
- Chalcosis, 562
- Chancre, 336
 - of penis, 815
 - of syphilis, 146
 - soft, 302
- Chancroid, 815
 - of vulva, 809
- Cheesy pneumonia, 558. See also *Tuberculous pneumonia.*
- Chemistry, pathological, 17
- Chemotaxis, 122
- Chilblain, 27
- Chlamydobacteriaceæ, 242
- Chlamydozoa, 363
- Chloasma, 993
- Chloroma, 188
 - of bone, 854
 - of bone-marrow, 466
- Chlorosis, 433
 - definition of, 433
 - etiology of, 434
 - pathological anatomy of, 434
 - physiology of, 435
- Choked disk, 981
- Cholangitis, 678
 - chronic, 679
 - results of, 680
 - suppurative, 679
- Cholecystitis, 680
- Cholelithiasis, 681
- Cholera, 330, 640
 - causes of, 332
 - conditions associated with, 642
 - definition of, 330
 - etiology of, 330
 - pathological anatomy of, 332, 640
 - physiology of, 332
- Cholesteatoma, 237
 - of middle ear, 989
 - of pia-arachnoid, 881
- Cholesterin deposits, 99
 - in urine, 766
- Choluria, 760
- Chondrocarcinoma of testicles, 823
- Chondrodystrophia fetalis, 837
- Chondroma, appearance of, 176
 - definition of, 176
 - etiology of, 176
 - nature of, 178
 - of bones, 853
 - of mammary glands, 832
 - of testicles, 822
 - seats of, 177
 - structure of, 177
- Chorion, 810
- Choroid, 965, 977
 - atrophy of, 977
 - hemorrhage in, 977
 - plexus, 922
 - calcification of, 923
 - hemorrhage into, 923
 - inflammation of, 922
 - pigmentary infiltration of, 923
 - tuberculosis of, 923
 - tumors of, 923
 - ruptures of, 977
 - syphilis of, 978
 - tuberculosis of, 978
 - tumors of, 978
 - wounds of, 977
- Choroiditis, 977
- Chromidrosis, 1008
- Chromogenesis of bacteria, 251
- Chyluria, 763
- Ciliary body, 965, 976
 - atrophy of, 976
 - cysts of, 977
 - syphilis of, 977
 - tuberculosis of, 977
- Circulation of blood, disturbances of, 56
- Circulatory system, diseases of, 467
- Cirrhosis, biliary, 668
 - Hanot's, 669
 - Laennec's, 665
 - of liver, 663
 - of pancreas, 688
 - pigmentary, 670
 - portal, 665
- Clap-threads, 769
- Cleft palate, 594
- Clitoris, elephantiasis of, 807
- Cloudy swelling, 79
 - definition of, 78
 - etiology of, 78
 - of kidneys, 737
 - pathological anatomy of, 78
 - physiology of, 79
 - seats of, 79
- Club-foot, 855
- Coagulating ferment, 248
- Coagulation necrosis, 107
 - definition of, 107
 - etiology of, 107
 - morbid physiology of, 108
 - of muscles, 868
 - pathological anatomy of, 107
- Coccacæ, 242
- Cocci, diseases due to, 273
- Coccidia, 377
- Coccidioides immitis, 348

- Coccidiosis, 348
 Coccidium bigeminum, 378
 cuniculi, 377
 Coccus, 243
 Cohnheim's emigration theory of inflammation, 118
 theory of tumor, 160
 Cold in etiology of disease, 26
 Colitis, 639
 mucous, 639
 Colloid degeneration, 90
 definition of, 90
 etiology of, 90
 microscopical appearance of, 90
 of arteries of brain, 901
 of pituitary body, 714
 pathological anatomy of, 90
 physiology of, 91
 goiter, 701
 Coloboma, 965, 974
 Colpitis, 806. See also *Vaginitis*.
 Column of Burdach, 932
 of Gowers, anterolateral, 932
 Columns of Goll and Burdach, 884
 Comedo, 1007
 Comotio cerebri, 25
 Communicable disease, 38
 methods of communication, 407
 Complement deviation, 269
 fixation, 269
 Compression of brain, 918
 Concrements, 99
 Concretions in uriniferous tubules, 740
 prostatic, 825
 Concussion of brain, 917
 Condyloma, 992
 acuminatum of penis, 815
 latum of syphilis, 146
 Congenital pneumonia, syphilitic, 563
 syphilis, 338
 theory of carcinoma, 220
 Congestion of lungs, 538
 passive, of esophagus, 609
 Conglutination, 69
 Conjunctiva, 964, 965
 anemia of, 965
 edema of, 966
 hemorrhage of, 966
 hyperemia of, 966
 syphilis of, 969
 tuberculosis of, 969
 Conjunctivitis, acute catarrhal, 966
 angular, 968
 follicular, 967
 Parinaud's, 968
 phlyctenular, 968
 pseudomembranous, 966
 purulent, 768
 vernal, 966
 Consumption, galloping, 569
 Contact infection, 408
 Contagious disease, 37
 Contre-coup, hemorrhage by, 917
 Cor bovinum, 495
 villosum, 500
 Cord, abnormal smallness of, 933
 Cord, anatomy of, 882
 development of, 882
 Corectopia, 974
 Corium, 990
 inflammation of, 1001
 Cornea, 964, 970
 leprosy of, 972
 ring abscess of, 972
 syphilis of, 972
 tuberculosis of, 972
 wounds of, 972
 Corns, 991
 Coronary artery, embolism of, 472
 thrombosis of, 472
 Corpora amylacea, 92
 Corpus callosum, 883
 fibrosum, 791
 luteum, 791
 Corpuscles, alteration of isotonicity of, 422
 dust-, 421
 red, 413
 diapedesis of, in inflammation, 123
 shadow, 421
 white, 414
 Cowper's glands, 828
 Cranioschisis, 888
 Craniotabes, 838
 Cretinism, 706
 Croup, false, 527
 Croupous enteritis, 633
 laryngitis, 528
 pneumonia, 280, 549. See also *Fibrinous pneumonia*.
 definition of, 280
 etiology of, 280
 Crusts, skin, 995
 Cryptophthalmia, 965
 Cryptorchismus, 817
 Crystalline lens, 973
 dislocation of, 974
 Currant-jelly clots, 471
 Cutaneous horns, 991
 Cutis, 990
 Cyanosis, 59
 chronic, with polycythemia and enlarged spleen, 428
 Cyclencephaly, 888
 Cyclopia, 965
 Cylindrical epithelioma, 229
 Cylindroids, 735
 Cylindroma, 202
 Cystadenoma of mammary glands, 833
 Cystic accumulations in lesser omental cavity, 690
 Cystin in urine, 766
 Cystinuria, 762
 Cystitis, 753
 chronic, 754
 mucopurulent, 754
 phlegmonous, 754
 pseudomembranous, 754
 Cystocele, 773
 vaginal, 805
 Cystoma of ovaries, 793
 papilliferous, of testicles, 823

Cystosarcoma of mammary glands, 833

Cysts, classification of, 231
 definition of, 231
 dermoid, 236
 epithelial, 232
 of bones, 854
 of ciliary body, 977
 of cornea, 972
 of dura mater, 873
 of eye, 969
 of Fallopian tubes, 802
 of iris, 976
 of kidneys, 745
 of Kobelt's tubes, 797
 of liver, 677
 of lungs, 584
 of mammary glands, 835
 of pancreas, 689
 of parovarium, 796
 of penis, 816
 of pituitary body, 714
 of prostate, 828
 of spleen, 449
 of testicles, 823
 of urethra, 770
 of uterus, 790
 of vagina, 807
 of vulva, 809
 proliferation, 232
 retention, 232
 sebaceous, 1007
 softening, 232
 tubo-ovarian, 802

Cytolysin, 268

Cytolysis, bacterial immunity as applied to, 266

DACTYO-ADENITIS, 970

Dacryo-cystitis, 970

Daughter stars, 151

Davainea madagascariensis, 390

Decidua, 810

reflexa, 810

serotina, 810

vera, 810

Decubitus, 993

Degeneration, albuminoid, 85

colloid, 90

fatty, 82

hyaline, 85

mucoid, 88

of intracardiac ganglia, 485

of mouth, 598

of nerves, 959

of spinal cord, secondary, 953

so-called, 78

Degenerative inflammation, 137

Deglutition pneumonia, 554

δ -granules, 417

Dengue, 360

Dermacentor occidentalis, 362

Dermatitis, 994

Dermatographia, 994

Dermatomycosis, 349

Dermatomyositis, 864

Dermoid cyst, 236

of ovaries, 795

of testicles, 823

Dextrinuria, 759

Diabète bronzé, 52, 102

Diabetes mellitus, 49

etiology of, 49

metabolism in, 51

pathogenesis, 50

pathological anatomy of, 52

Diaceturia, 760

Diapedesis, 61

of red corpuscles in inflammation, 123

Diastatic ferments, 248

Diastematomyelia, 933

Dibothriocephalus cordatus, 394

latus, 393

geographical distribution, 394

Dicrocoelium lanceatum, 381

Dilatation of bile-ducts, 681

of bronchi, 535

of esophagus, 611

of Fallopian tubes, 798

of heart, 494

of intestines, 627

of lymphatic vessels, 521

of stomach, 621

atonic, 621

of ureter, 748

of uterus, 775

of veins, 519

Diphtheria, definition of, 285

distribution of bacilli in, 287

etiology of, 285

internal lesions in, 287

mixed infection in, 286

of animals, 287

of pharynx, 606

of vulva, 809

pathological anatomy of, 287

physiology of, 288

predisposing causes of, 286

Diphtheria-like bacilli, 288

Diphtheritic inflammation, 131

laryngitis, 528

rhinitis, 525

salpingitis, 800

Diplococcus pneumoniae, 280, 549

in other diseases, 282

Diplogonoporus grandis, 394

Dipylidium caninum, 390

Direct infection, 408

Disease, age in, 19

cold in, 20

conditions of life in, 20

definition of, 17

determining causes of, 23

etiology, 19

foot-and-mouth, 362

heat in, 20

idiosyncrasy in, 20

injury in, 20

nutrition in, 20

pathologic disposition to, 20

physical forces in, 20

poisons in, 20

- Disease, predisposing factors, 19
 race in, 20
 sex in, 20
 symptoms of, 18
 transmission of, by animals, 410
 by food, 409
 by human beings, 410
 by insects, 409
 by soil, 409
 by unknown methods, 411
 by water, 409
 indirect, 409
 Diseases, animal parasites from, 364
 communicable, methods of transmission, 407
 due to bacillary forms, 285
 to bacteria, 273
 to cocci, 273
 to higher bacteria, 341
 to spirilla, 330
 to spirochetes, 334
 hemorrhagic, 349
 infectious, of unknown origin, 351
 of blood, 412
 suppurative, 273
 Dissecting aneurysm, 515
 Distomum hæmatobium, 382
 hepaticum, 380
 Diverticula of esophagus, 611
 Dropsical infiltration, 95
 of liver, 661
 Dropsy of joints, 856
 of peritoneum, 692
 Ductless glands, carcinoma of, 711
 diseases of, 699
 Ductus Botalli, patulous, 470
 Dumdum fever, 370
 Duodenitis, 635
 Dura mater, cysts of, 873
 fatty infiltration of, 928
 hemorrhage from, 870, 928
 sarcoma of, 929
 sinus thrombosis of, 870
 syphilis of, 872, 929
 tuberculosis of, 872
 tumors of, 872, 929
 Dust-cells, 560
 Dust-corpuses, 421
 Dust-embolism, 64
 Dyscoria, 974
 Dyscrasia, constitutional, 159
 in carcinoma, 221
 Dysentery, 639
 amebic, 640
 bacillary, 639
 bacillus of, 297
 Dysmenorrhea membranacea, 776
 Dyspepsia, 616
- EAR, 984
 anatomy of, 984
 congenital defects of, 985
 external, 985
 frost-bite of, 985
 mycosis of, 986
- Ear, external, syphilis of, 986
 tuberculosis of, 986
 tumors of, 986
 internal, circulatory disturbances of, 989
 inflammation of, 989
 middle, cholesteatoma of, 989
 hemorrhage of, 987
 hyperemia of, 987
 syphilis of, 988
 tuberculosis of, 988
 tumors of, 989
 Ecchymosis, 63
 Echinococcus cysts, 391
 of testicles, 824
 seats of, 393
 Echinorhynchus gigas, 404
 Ectatic aneurysm, 513
 Ecthyma, 995
 Ectoplasm, 244
 Eczema, 997
 Edema, alterations of blood in, 74
 of tissue liquids in, 75
 angioneurotic, 74
 decreased tissue elasticity in, 73
 definition of, 72
 direct filtration in, 73
 etiology of, 72
 in inflammation, 125
 in nephritis, 736
 increased blood-pressure in, 73
 permeability of capillary walls in, 74
 malignant, 311
 obstruction of lymphatic circulation in, 74
 of conjunctiva, 966
 of eyelids, 983
 of kidneys, 719
 of larynx, 527
 of lungs, 540
 of mucosa of intestines, 632
 of nasal cavities, 524
 of nerves, 958
 of pharynx, 602
 of pia-arachnoid, 874
 of skin, 994
 of vulva, 808
 osmosis in, 73
 pathological anatomy of, 75
 results of, 75
 Edematous inflammation, 130
 Ehrlich's side-chain theory of immunity, 262
 Eimeria hominis, 378
 Electrical influences in etiology of disease, 29
 Elephantiasis, 992
 of clitoris, 807
 of labiæ, 807
 of scrotum, 815
 of vulva, 809
 Emboli, sources and nature of, 64
 Embolism, 64
 dust-, 64
 fat-, 64
 infectious, 67

- Embolism of arteries of muscles, 863
 of brain, 908
 of coronary artery, 472
 of lungs, 542
 of mesenteric arteries, 632
 of portal vein, 656
 of renal arteries, 719
 of spermatic artery, 818
 of splenic artery, 445
 paradoxical, 65
 results of, 65
 retrograde, 65
 seats of, 64
 Emigration of leukocytes, 61
 Emphysema, infectious, 312
 of lungs, atrophic, 545
 bullous, 545
 interstitial, 543
 vesicular, 544
 vicarious, 544
 senile, 546
 Empyema of gall-bladder, 680
 purulent, 589
 Encephalitis, 910
 acute parenchymatous, 911
 chronic, 914
 primary acute hemorrhagic, 914
 simple acute focal, 911
 suppurative, 912
 Encephalocele, 888
 Encephalomalacia, 909
 End-arteries, 66
 Endarteritis, 505
 chronica deformans, 507
 Endemic disease, 38
 Endocarditis, acute, 473
 changes in other organs in, 479
 etiology of, 473
 lesions in other organs in, 477
 pathological anatomy of, 474
 results of, 476
 chronic, 477
 changes in heart in, 478
 etiology of, 477
 malignant, 477
 pathological anatomy of, 477
 pathological physiology of, 479
 recurrent, 477
 subacute, 477
 Endocardium, diseases of, 472
 inflammation of, 473
 Endometritis, 777
 acute catarrhal, 777
 chronic, 777
 of cervix, 778
 decidualis, 811
 exfoliativa, 776
 glandularis, 777
 interstitialis, 777
 Endoplasm, 244
 Endosporium, 244
 Endothelioma, 203
 of lymphatic glands, 462
 of pia-arachnoid, 880
 of spleen, 449
 Enophthalmos, 983
 Enostoses of bones, 853
 Entamoeba buccalis, 366
 histolytica, 640
 description of, 364
 pathogenesis of, 366
 urinalis, 366
 Enteritis, catarrhal, 633
 chronic, 635
 croupous, 633
 follicular, 633, 635
 pathological physiology of, 635
 pseudomembranous, 634
 suppurative, 634
 toxic, 633
 ulcerative, 634
 Enterocystoma of intestines, 627
 Enterogenic albumosuria, 761
 Enteroliths, 653
 Enteromycosis of intestines, 648
 Enterorrhagia, 63
 Enzymes, 247
 Eosinophile granules, 417
 Eosinophiles, 416
 Epencephalon, 883
 Ependymitis of ventricles, 923
 Epicanthus, 965
 Epidemic disease, 38
 Epidermis, 990
 Epididymitis, 818
 acute, 768, 819
 Epiphysis cerebri, 715
 Episcleritis, 972
 Epispadias, 814
 Epistaxis, 63, 524
 Epithelial cysts, appearance of, 232
 definition of, 232
 etiology of, 232
 nature of, 234
 seats of, 233
 structure of, 233
 tumors, 212
 Epithelioid cells, 141
 Epithelioma adenoides, 991
 contagiosum, 1005
 cylindrical, 229
 of penis, 815
 of skin, benign cystic, 1006
 squamous, 227
 of-skin, 1006
 Epithelium, regeneration of, 151
 ϵ -granules, 418
 Epulis, 196, 600
 Ergot, poisoning from, 34
 Erosions of uterus, 779
 Erysipelas, 1002
 Erythema, 995
 Erythrasma, 1004
 Erythroblasts, 421
 primitive, 419
 Erythrocytes, 413
 nucleated, 421
 skeletal, 414
 Escharotics, action of, 31
 Esophagitis, catarrhal, 610
 chronic, 610
 phlegmonous, 610

- Esophagitis, pseudomembranous, 610**
 ulcerative, 610
Esophagomalacia, 612
Esophagus, 609
 anemia of, 609
 congenital defects of, 609
 dilatation of, 611
 diverticula of, 611
 hyperemia of, 609
 inflammation of, 610
 passive congestion of, 609
 perforation of, 611
 rupture of, 611
 stenosis of, 610
 syphilis of, 612
 tuberculosis of, 612
 tumors of, 612
 typhoid ulceration of, 612
Etat crible, 910
Ethylendiamin, 37
Etiology, definition of, 17
 of disease, 19
Eumycetes, 242
Eunuchism, 816
Eustachian tube, inflammation of, 989
Eustrongylus gigas, 405
Exophthalmos, 983
Exosporium, 244
Exostoses of bones, 853
Exstrophy of bladder, 752
Extra-uterine pregnancy, 803
 etiology of, 803
 pathological anatomy of, 803
 varieties of, 803
Eye, anatomy of, 964
 anterior chamber of, 972
 cysts of, 969
 tumors of, 969
Eyelids, 983
 edema of, 983
 ptosis of, 983
 congenital, 965
 tumors of, 983

FALLOPIAN tubes, anatomy of, 797
 carcinoma of, 802
 changes of position of, 797
 congenital abnormalities of, 797
 cysts of, 802
 development of, 797
 dilatation of, 798
 fibroma of, 802
 fibromyoma of, 802
 hematoma of, 798
 hemorrhages into, 798
 hyperemia of, 798
 lipoma of, 802
 sarcoma of, 802
 stenosis of, 798
 syncytioma malignum of, 802
 syphilis of, 802
 tuberculosis of, 801
False aneurysm, 517
Farcy, 305
Fasciola hepatica, 380

Fat crystals in urine, 766
 embolism, 64
 metabolism of, 40
 necrosis, 111
 of pancreas, 686
Fat-splitting ferments, 248
Fatty casts, 735
 degeneration, 82
 definition of, 82
 etiology of, 82
 microscopic appearances of, 83
 of heart, 483
 of kidneys, 738
 of liver, 659
 of muscles, 867
 of pericardium, 504
 of prostate, 825
 of stomach, 620
 of suprarenal bodies, 709
 of testicles, 817
 of uterus, 783
 of veins, 518
 pathological anatomy of, 83
 physiology of, 84
 seats of, 84
 infiltration, 80
 definition of, 80
 etiology of, 80
 of bone-marrow, 463
 of dura mater, 928
 of heart, 482
 of kidneys, 738
 of liver, 658
 of lymph-glands, 453
 of mammary glands, 831
 of muscles, 868
 pathological anatomy of, 81
 physiology of, 81
 seats of, 81
Favus, 1004
Ferment theory of immunity, 259
Fermentation, 247
Ferments, coagulating, 248
 diastatic, 248
 effects of, 249
 fat-splitting, 248
 hydrolytic, 248
 inverting, 248
 nitrifying, 248
 of bacteria, 247
 oxidizing, 248
 proteolytic, 248
Fetal membranes, 810
 hemorrhage from, 810
Fever, conservative effects of, 54, 55
 definition of, 53
 etiology of, 54
 nature of, 53
 paratyphoid, 646
 pathological anatomy of, 55
 physiology of, 55
 typhoid, 642
Fibrin-ferment, 69
Fibrinogen, 69
Fibrinous bronchitis, 533
 inflammation, 131

- Fibrinous pleuritis, 587
 pneumonia, 549
 Fibrinuria, 762
 Fibro-adenoma of bladder, 758
 of mammary glands, 831
 Fibroid phthisis, 569, 573
 Fibroids of uterus, 784
 Fibroma, appearance of, 170
 definition of, 169
 etiology of, 169
 intracanalicular, 171
 nature of, 172
 of bladder, 758
 of bones, 853
 of brain, 921
 of Fallopian tubes, 802
 of kidneys, 741
 of larynx, 530
 of mammary glands, 831
 of pancreas, 698
 of skin, 1005
 of testicles, 822
 of vagina, 807
 of vulva, 809
 seats of, 170
 secondary changes in, 172
 structure of, 171
 Fibromyoma of Fallopian tubes, 802
 Fibromyxoma of vulva, 809
 Fibrosis, arteriocapillary, 507
 general, 138
 Fibrous connective tissue, regeneration
 of, 151
 pneumonia, 560
 Filaria bancrofti, 402
 medinensis, 401
 Filariæ, varieties of, 404
 Filariasis, 404
 Filterable viruses, 351
 Fissure, anal, 634
 Fistula in ano, 639
 Flagella, 244
 Fleshy moles, 811
 Fluke-worms, 380, 384
 Focal necroses, 112
 Follicular cysts of ovaries, 793
 enteritis, 633
 Food, diminished supply of, 39
 increased supply of, 40
 transmission of disease, 409
 Foot-and-mouth disease, 362, 595
 Foreign bodies, cysts from, 232
 in bladder, 755
 in bronchi, 537
 in intestines, 652
 Foreign-body tubercle, 143
 Fowl tuberculosis, 325
 Fracture, comminuted, 839
 compound, 839
 definition of, 839
 repair of, 839
 Fragilitas ossium, 848
 Frambesia, 341
 Freckles, 993
 Friedberger's anaphylotoxin theory of in-
 fection, 271
 Friedrich's ataxia, 948
 Fungus, benign, of testicles, 819
 syphilitic, of testicles, 822
 Furuncles, 135, 1001

 GALACTORRHEA, 831
 Galen's definition of inflammation, 118
 Gall-bladder, contraction of, 681
 empyema of, 680
 inflammation of, 680
 Galloping consumption, 569
 Gall-stones, etiology of, 681
 pathological anatomy of, 682
 structure of, 682
 γ -granules, 417
 Ganglia of spinal nerves, diseases of, 958
 of tendon-sheaths, 862
 Gangrene, 105, 112
 definition of, 112
 dry, 112
 moist, 113
 of lung, 565
 of vulva, 809
 primary, 112
 secondary, 112
 Gangrenous inflammation, 137
 stomatitis, 597
 Gastrectasia, 621
 Gastric ulcer, 617
 etiology of, 617
 pathological anatomy of, 618
 Gastritis, acute, 614
 atrophic, 616
 chronic, 615
 hypertrophic, 616
 interstitial, 616
 pathological physiology of, 616
 pseudomembranous, 614
 ulcerative, 615
 Gastro-intestinal tract, diseases of, 594
 Gastromalacia, 620
 Gastroptosis, 621
 Genu valgum, 855
 varum, 855
 Germinal cells, 882
 Giant growth of bones, 841
 Giant-celled sarcoma, 195
 Giant-cells, classification of, 128
 in inflammation, 125
 Langhans', 142
 Gigantism, 158
 Gin-drinkers' liver, 665
 Glanders, 148, 526
 definition of, 304
 etiology of, 304
 hemolymph, 451
 lymphatic, 450
 of larynx, 529
 of lungs, 579
 of muscles, 869
 of skin, 1003
 pathological anatomy of, 305
 physiology of, 305
 Glandular carcinoma, 229
 organs, regeneration of, 154

- Glans penis, inflammation of cavernous
bodies of, 815
of mucous membrane of, 814
- Glaucoma, 980
- Gleet, 769
- Glioma, appearance of, 205
definition of, 205
etiology of, 205
ganglionare, 207
appearance of, 208
definition of, 207
etiology of, 207
nature of, 208
structure of, 208
nature of, 206
of brain, 919
of retina, 206
of spinal cord, 957
of suprarenal bodies, 711
seats of, 205
structure of, 206
- Glossitis, hypertrophic nodular, 888
- Glomerulonephritis, acute, 722
- Glossitis, 594, 598
- Glucosuria, alimentary, 48, 759
causes of, 49
from excessive hepatic glycolysis, 49
renal, 51
- Glycogenic infiltration, 94
definition of, 94
etiology of, 94
of kidneys, 739
pathological anatomy of, 95
physiology of, 95
reaction, 423
- Glycolysis, excessive hepatic, glucosuria
from, 49
- Goiter, adenomatous, 702
colloid, 701
cystic, 700
etiology of, 700
fibrous, 701
mechanical effects of, 704
parenchymatous, 700
pathological anatomy of, 700
secondary changes in, 704
vascular, 701
- Goll, columns of, 884
- Gonococcus, 279
cultivation of, 279
pathogenicity of, 279
- Gonorrhea, 767
definition of, 278
etiology of, 278
pathological anatomy of, 279
physiology of, 280
- Gonorrheal arthritis, 769
tenosynovitis, 769
urethritis, 770
- Gout, 46, 860
etiology of, 46
pathogenesis of, 47
pathological anatomy of, 46
- Gouty tophi, 860
- Gowers, anterolateral column of, 932
- Granular casts, 735
- Granular disintegration, 79
- Granulation tissue in inflammation, 128
- Granules of leukocytes, 417
- Granuloma, infectious, 141
pyogenicum, 349
- Graves' disease, 707
- Grawitz, granular degeneration of, 26
- Gruber-Durham phenomenon in typhoid
fever, 292
- Gumma, 1003
of syphilis, 146
- HAIR, 1008
- Hair-follicles, inflammation of, 1000
- Hanot's cirrhosis, 669
- Hansemann's theory of tumors, 161
- Harelip, 594
- Healing by first intention, 137
by immediate union, 137
by second intention, 138
- Heart, 467
abnormality in size of, 468
of position of, 468
actinomycosis of, 497
amyloid infiltration of, 482
anatomical considerations of, 467
aneurysm of, 496
atrophy of, 493
changes in, in chronic endocarditis, 478
congenital diseases of, 468
deformities of, 468
development of, 467
defective, 468
dilatation of, 494
fatty degeneration of, 483
infiltration of, 482
hyaline degeneration of, 482
hypertrophy of, 494
hypoplasia of, 492
new-growths of, 497
overaction of, 57
parasites in, 498
parenchymatous degeneration of, 481
pathological physiology of, 470
primary tumors of, 497
rupture of, 497
secondary tumors of, 497
syphilis of, 497
thrombosis of cavities of, 471
tuberculosis of, 497
valvular defects of, 470
weak, 56
wounds of, 497
- Heart-muscle, anemia of, 481
hemorrhages in, 481
hyperemia of, 481
inflammation of, 486
pathological physiology of, 486
segmentation of fibers of, 485
- Heat in etiology of disease, 25
- Heberden's nodes, 859
- Hemangioma, appearance of, 182
definition of, 182
etiology of, 182
nature of, 184

- Hemangioma**, seats of, 182
 structure of, 183
Hematemesis, 63
Hematocele, retro-uterine, 776
Hematochyluria, 763
Hematocolpos, 805
Hematogenic albumosuria, 762
 purulent pneumonia, 563
 tuberculosis, 575
Hematogenous jaundice, 684
 pigmentation, 101
 microscopic appearance of, 103
Hematoidin, 870
 in urine, 766
Hematoma, 63
 auris, 985
 of Fallopian tubes, 798
 of muscles, 868
 of vulva, 808
Hematometra, 775, 805
Hematomyelia, 933, 938
Hematosalpinx, 801
Hematuria, 762
Hemicrania, 888
Hemochromatosis, 102
Hemocytolysis, 426
Hemoglobin in urine, 766
Hemoglobinemia, 426
Hemoglobinuria, 762
 paroxysmal, 763
Hemokonia, 421
Hemolymph glands, 451
Hemolysis, 112
Hemolytic ictero-anemia, 438
Hemopericardium, 498
Hemophilia, 62
Hemoptysis, 63
Hemorrhage, 60
 by contre-coup, 917
 causes of, 62
 cerebral, 904
 massive, 905
 punctate, 904
 classification of, 63
 from bones, 841
 from diseases of blood-vessels, 62
 from dura mater, 928
 from fetal membranes, 810
 from increase of blood-pressure, 62
 from mammary glands, 829
 from ovaries, 791
 in chorioid, 977
 in heart-muscle, 481
 in muscles, 863
 in pia-arachnoid, 874
 in spleen, 445
 into choroid plexus, 923
 into Fallopian tubes, 798
 into joints, 856
 into skin, 994
 into vaginal walls, 806
 into vitreous humor, 974
 leukocytosis from, 429
 neuropathic, 62
 of bladder, 753
 of bronchi, 532
 of conjunctiva, 966
 of dura mater, 870
 of intestines, 631
 of kidneys, 719
 of larynx, 527
 of lungs, 540
 of middle ear, 987
 of mouth, 594
 of nasal cavities, 524
 of nerves, 958
 of pancreas, 685
 of pericardium, 498
 of peritoneum, 691
 of pharynx, 602
 of pia-arachnoid, 929
 of retina, 970
 of spinal cord, 937
 of stomach, 613
 of suprarenal bodies, 710
 of uterus, 776
 petechial, of pleura, 585
 results of, 63
 traumatic, 62
Hemorrhagic diathesis, 62
 diseases, 349
 infarcts, 63
 of lungs, 541
 inflammation, 135
 pancreatitis, acute, 687
 pleuritis, 590
Hemorrhoids, 632
Hemosiderosis, 670
Hemosporidia, 372
Hemothorax, 585
Hepatitis, 662
 interstitial, acute, 662
 chronic, 663
 parenchymatous, 662
Hepatogenous pigmentation, 104
Hereditary congenital pathological conditions, 22
Heredity in carcinoma, 221
 in etiology of disease, 21. See also *Inheritance*.
 pathologic conditions of later life depending on, 22
Hermaphroditism, 239, 814
Hernia, etiology of, 627
 external, varieties of, 628
 internal, varieties of, 628
 of intestine, 627
 pathological anatomy of, 628
 strangulated, 629
Herpes, 996
Heterochromia, 974
Heterotopia of gray matter of spinal cord, 933
Hippuric acid in urine, 765
Histoplasmosis, 371
Hives, 994
Hob-nail liver, 665
Hodgkin's disease, 441
 of lymphatic glands, 461
 of spleen, 449
Hordeolum, 983
Horseshoe-kidney, 717

- Human transmission of disease, 410
 Hutchinson's teeth, 339, 601
 Hyaline casts, 734
 degeneration, 85
 definition of, 85
 etiology of, 86
 of arteries of brain, 901
 of heart, 482
 of lymph-glands, 453
 of muscles, 868
 of pericardium, 504
 of spinal cord, 936
 of spleen, 448
 pathological anatomy of, 86
 physiology of, 88
 seats of, 87
 Hydatid moles, 813
 Hydatids of Morgagni, 802
 Hydradenitis, 1008
 Hydremia, 425
 Hydrocele funiculi cystica, 820
 spermatici, 820
 processus vaginalis, 820
 spermatica, 820
 Hydrocephalus, acquired, 927
 acute, 879
 acquired internal, 927
 chronic, 927
 external, 910, 927
 fetal, 888
 internus, congenital, 925
 partial, 927
 Hydrolytic ferments, 248
 Hydroma duræ matris, 871
 Hydrometra, 775
 Hydromyelia, 933, 934
 Hydropericardium, 498
 Hydrops articulum, 857
 e vacuo, 910
 omenti, 692
 Hydrorrhachis, 933
 Hydrorrhœa gravidarum, 811
 Hydrosalpinx, 801
 Hydrothionuria, 761
 Hydrothorax, 585
 Hygroma, 874
 Hymenolepis diminuta, 389
 nana, 389
 Hyperemia, active, 59
 of lungs, 538
 arterial, 59
 collateral, 59
 local, 59
 neuroparalytic, 59
 neurotonic, 59
 of bladder, 753
 of bones, 841
 of brain, 903
 of bronchi, 532
 of conjunctiva, 966
 of dura mater, 870
 of esophagus, 609
 of Fallopian tubes, 798
 of heart-muscle, 481
 of intestines, 631
 of joints, 856
 Hyperemia of kidneys, 718
 of larynx, 527
 of liver, 654
 of mammary glands, 829
 of middle ear, 987
 of mouth, 594
 of muscles, 863
 of nasal cavities, 524
 of ovaries, 791
 of pancreas, 685
 of pericardium, 498
 of peritoneum, 691
 of pharynx, 602
 of pia-arachnoid, 874, 929
 of pleura, 585
 of retina, 973
 of skin, 994
 of spinal cord, 937
 of spleen, 444
 of stomach, 613
 of testicles, 818
 of uterus, 775
 of uveal tract, 975
 of vagina, 806
 of vulva, 808
 passive, 59
 of lungs, 538
 venous, 59
 Hyperglucemia, 48
 Hyperidrosis, 1007
 Hyperinosis of plasma, 424
 Hyperkeratosis, 998
 Hypernephroma of kidney, 742
 of suprarenal bodies, 711
 Hyperplasia of mucous membrane of
 uterus, 783
 of placenta, 812
 Hyperplastic perihepatitis, 696
 Hypersusceptibility, 270
 Hyperthyroidism, 703, 707
 Hypertrichosis, 1008
 Hypertrophic gastritis, 616
 Hypertrophy, 157
 definition of, 157
 etiology of, 157
 of bone-marrow, 464
 of bones, 841
 of brain, 889
 of cervix uteri, 783
 of heart, 494
 of kidneys, 737
 of liver, 670
 of lungs, 543
 of lymph-glands, 452
 of mammary glands, 830
 of muscles, 863
 of pericardium, 503
 of pituitary body, 713
 of prostate, 825
 of skin, 991
 of testicles, 817
 of tonsils, 605
 of uterus, 783
 pathological anatomy of, 158
 physiology of, 158
 Hypinosis of plasma, 424

- Hypophysis cerebri, 712. See also *Pituitary body*.
- Hypoplasia, definition of, 75
- of bones, 847
 - of brain, 889
 - of cerebellum, 889
 - of cerebral hemispheres, 889
 - of heart, 492
 - of pericardium, 503
 - of testicles, 816
- Hypopyon, 970
- Hypospadias, 814
- Hypostatic congestion, 56, 59
- pneumonia, 554, 557
- ICHTHYOSIS, 992
- Icterus, 683. See also *Jaundice*.
- Idiosyncrasy in disease, 20
- Ileum, inflammation of, 635
- Immune bodies, chemistry of, 272
- Immunity, 19
- acquired bacterial, 255
 - toxin, 256, 260
 - active acquired, 256
 - alexin theory of, 256
 - antibacterial, 269
 - antitoxic, 268
 - bacterial, 265
 - agglutination theory of, 259
 - as applied to bacteriolysis, 266
 - to cytolysis, 266
 - natural, 255
 - bacteriolytic theory of, 257
 - definition of, 255
 - Ehrlich's side-chain theory of, 263
 - ferment theory of, 259
 - natural toxin, 255, 259
 - opsonin theory of, 258
 - passive acquired, 256
 - phagocytosis theory of, 257
 - theories of, 256
 - varieties of, 255
- Impetigo, 996
- Inanition, 39
- Indicanuria, 760
- Indigestion, 616
- Indigo in urine, 766
- Indirect transmission of disease, 409
- Indolent ulcer, 134
- Indurative pancreatitis, chronic, 688
- Infantilism, 76
- Infarction, 66
- Infarcts, formation of, 66
- hemorrhagic, of lungs, 541
 - pulmonary, 67
 - subsequent changes in, 67
- Infection, 251, 253
- Friedberger's anaphylatoxin theory of, 271
 - paracolon, 294
 - paratyphoid, 294
- Infectious disease, 37
- emphysema, definition of, 312
 - etiology of, 312
 - pathological anatomy of, 313
- Infectious granulomata, 141
- theory of carcinoma, 220
- Infestation, 251
- Infiltration, amyloid, 91
- dropsical, 95
 - fatty, 80
 - glycogenic, 94
 - so-called, 78
- Inflammation, 117
- catarrhal, 135
 - changes in blood-vessels in, 120
 - chemical processes involved in, 125
 - chronic, 137
 - Cohnheim's emigration theory of, 118
 - definition of, 117
 - degenerative, 137
 - changes in tissues in, 129
 - diapedesis of red corpuscles in, 123
 - diphtheritic, 131
 - edema in, 125
 - edematous, 130
 - etiology, 130
 - exudation in, 121
 - of liquids in, 125
 - fibrinous, 131
 - fibroblastic cells in, 127
 - Galen's definition, 118
 - gangrenous, 137
 - giant-cells in, 125
 - granulation tissue in, 128
 - hemorrhagic, 135
 - historical note on, 118
 - influence of nervous system in, 121
 - large mononuclear phagocytic cells in, 124
 - necrotic, 137
 - of arteries, 505. See also *Arteritis*.
 - of biliary ducts, 678. See also *Cholangitis*.
 - of bladder, 753. See also *Cystitis*.
 - of bone-marrow, 465. See also *Osteomyelitis*.
 - of bones, 842. See also *Ostitis*.
 - of brain substance, 910. See also *Encephalitis*.
 - of bronchi, 532. See also *Bronchitis*.
 - of bursæ, 862
 - of cecum, 636
 - of choroid, 977
 - plexus, 922
 - of ciliary body, 976
 - of conjunctiva, 966. See also *Conjunctivitis*.
 - of corium, 1001
 - of cornea, 970. See also *Keratitis*.
 - of dura mater, 870. See also *Pachymeningitis*.
 - of endocardium, 473. See also *Endocarditis*.
 - of epididymis, 818
 - of esophagus, 610. See also *Esophagitis*.
 - of Eustachian tube, 989
 - of external ear, 985
 - of eyelids, 903
 - of Fallopian tubes, 799

- Inflammation of gall-bladder, 680
 of hair-follicles, 1000
 of heart-muscle, 486. See also *Myocarditis*.
 of ileum, 635
 of internal ear, 989
 of intestines, 633. See also *Enteritis*.
 of iris, 975
 of joints, 856. See also *Arthritis*.
 of kidney, 720. See also *Nephritis*.
 pelvis, 749
 of liver, 662. See also *Hepatitis*.
 of lungs, 548. See also *Pneumonia*.
 of lymphatic vessels, 521
 of lymph-glands, 454. See also *Lymphadenitis*.
 of mammary glands, 829. See also *Mastitis*.
 of middle ear, 987. See *Otitis media*.
 of mouth, 594. See also *Stomatitis*.
 of muscles, 864. See also *Myositis*.
 of nails, 1008
 of nasal cavities, 525
 of nerves, 960. See also *Neuritis*.
 of nipples, 830
 of ovaries, 791
 of pancreas, 687. See also *Pancreatitis*.
 of pericardium, 498. See also *Pericarditis*.
 of peritoneum, 693. See also *Peritonitis*.
 of pharynx, 602. See also *Pharyngitis*.
 of pia-arachnoid, 874, 930. See also *Leptomeningitis*.
 of pituitary body, 713
 of placenta, 811
 of pleura, 586. See also *Pleuritis*.
 of prostate, 824. See also *Prostatitis*.
 of pulp of teeth, 601
 of rectum, 639
 of retina, 979
 of salivary glands, 608. See also *Parotitis*.
 of sebaceous glands, 1000
 of skin, 994
 of spinal cord, 938. See also *Myelitis*.
 of spleen, 445. See also *Splenitis*.
 of stomach mucosa, 615. See also *Gastritis*.
 of subcutis, 1001
 of suprarenal bodies, 711
 of testicles, 818. See also *Orchitis*.
 of thymus gland, 712
 of thyroid gland, 700
 of tongue, 594. See also *Glossitis*.
 of trachea, 531
 of tunica vaginalis, 818
 of ureter, 750
 of uterus, 777
 of vagina, 806. See also *Vaginitis*.
 of vas deferens, 820
 of veins, 518. See also *Phlebitis*.
 of vitreous humor, 974
 of vulva, 808
 parenchymatous, 136
 pathological physiology of, 139
- Inflammation, phagocytosis in, 123
 phenomena of, in avascular tissues, 119
 in vascular tissues, 118
 phlegmonous, 134
 productive, 137
 proliferative changes in, 127
 in parenchymatous cells, 129
 pseudomembranous, 131, 287
 resolution after, 140
 rôle and fate of leukocytes in, 123
 round-cell infiltration in, 127
 secondary cellular degenerations in, 129
 serous, 130
 special forms of, 130
 specific, 141
 suppurative, 132
 types of, 130
 vascular theories of, 118
 Virchow's theory of, 118
 Influenza, definition of, 298
 etiology of, 298
 pathological anatomy of, 298
 Infusoria, 379
 Inheritance, blended, 23
 collateral, 21
 cumulative, 23
 diathetic, 23
 direct, 21
 familial, 23
 in etiology of disease, 21
 indirect, 21
 particulate, 23
 racial, 23
 reversionary, 23
 Insect transmission of disease, 409
 with cycle of development in intermediate host, 410
 venom, poisoning from, 34
 Interstitial gastritis, 616
 pregnancy, 803
 Intestinal obstruction, 629
 sand, 653
 Intestines, abnormalities of, 626
 actinomycosis of, 648
 amyloid infiltration of mucosa of, 631
 anthrax of, 648
 atrophy of mucosa of, 631
 carcinoma of, 649
 congenital abnormalities in position of, 627
 enlargement of, 626
 dilatation of, 627
 distortion of, 626
 edema of mucosa of, 632
 enterocystoma of, 627
 enteromycosis of, 648
 foreign bodies in, 653
 hemorrhage of, 631
 hernia of, 627
 hyperemia of, 631
 inflammation of, 633. See also *Enteritis*.
 internal strangulation of, 629
 intussusception of, 629
 invagination of, 629
 narrowing of, 626

Intestines, parasites of, 651
 pigmentation of mucosa of, 631
 rupture of, 652
 sarcoma of, 648
 stenosis of, 627
 syphilis of, 647
 total absence of, 626
 tuberculosis of, 646
 tumors of, 648
 volvulus of, 629
 Intoxication, 253
 Intracardiac ganglia, degeneration of, 485
 Intussusception of intestine, 629
 Invagination of intestines, 629
 Inversion of uterus, 773
 Inverting ferments, 248
 Iodophilia, 423
 Iridocyclitis, 976
 Iris, 965, 974
 atrophy of, 974
 congenital abnormalities of, 974
 cysts of, 976
 syphilis of, 975
 tuberculosis of, 975
 Iritis, 975
 Irritation cells, 416
 Islands of Langerhans, diseases of, 686

JAUNDICE, 683
 catarrhal, 635, 684
 etiology of, 683
 hematogenous, 684
 pathological anatomy of, 684
 Joints, ankylosis of, 855
 diseases of, 855
 distortions of, 855
 dropsy of, 856
 hemorrhage into, 856
 hyperemia of, 856
 luxation of, 855
 syphilis of, 861
 tuberculosis of, 860
 etiology of, 861
 pathological anatomy of, 861
 secondary disorders, 861
 tumors of, 862

KALA-AZAR, 370
 Karyokinesis, 150
 altered, in necrotic cells, 115
 Karyokinetic figures, 421
 Karyolysis in cellular necrosis, 114
 Karyomitosis, 150
 Karyorrhexis in cellular necrosis, 114
 Keloid, 1005
 Keratitis, 970
 bullous, 971
 interstitial, 970
 phlyctenular, 971
 suppurative, 972
 ulcerative, 971
 Keratomalacia, 972
 Kidney, adenoma of, 744
 amyloid infiltration of, 739

Kidney, anemia of, 718
 animal parasites of, 747
 atrophy of, 737
 bacteria in, 747
 calcification of, 739
 calculi in pelvis of, 749
 carcinoma of, 744
 cloudy swelling of, 737
 congenital anomalies of, 717
 cysts of, 745
 edema of, 719
 embolism of arteries of, 719
 fatty contracting, 726
 degeneration of, 738
 infiltration of, 738
 fibroma of, 741
 glycogenic infiltration of, 739
 hemorrhage of, 719
 hyperemia of, 718
 hypernephroma of, 742
 hypertrophy of, 737
 inflammation of, 720. See also *Nephritis*.
 large white, 726
 lipoma of, 741
 malposition of, 717
 parasites of, 751
 parenchymatous degeneration of, 737
 pelvis, inflammation of, 749
 red granular, 730
 sarcoma of, 743
 secondary tumors of, 745
 syphilis, 741
 thrombosis of veins of, 719
 tuberculosis of, 741, 750
 tumors of, 751
 Knock-knee, 855
 Kobelt's tubes, cysts of, 797
 Kraurosis vulvæ, 806

LABIÆ, elephantiasis of, 807
 Lachrymal organs, 970
 Lactosuria, 759
 Laennec's cirrhosis, 665
 Lambliæ intestinalis, 368
 Landry's ascending paralysis, 943
 Langerhans, diseases of islands of, 686
 Langhans' giant-cell, 142
 Lardacein, 91
 Lardaceous disease, 91
 Laryngitis, catarrhal, acute, 527
 chronic, 527
 croupous, 528
 diphtheritic, 528
 edematous, 528
 Larynx, anatomical considerations of, 526
 anemia of, 527
 atrophy of, 529
 carcinoma of, 530
 congenital abnormalities of, 526
 edema of, 527
 fibroma of, 530
 glanders of, 529
 hemorrhages of, 527
 hyperemia of, 527

- Larynx, inflammation of, 527. See also *Laryngitis*.
 lepra of, 529
 papilloma of, 529
 parasites of, 530
 stenosis of, 529
 syphilis of, 529
 tuberculosis of, 528
- Lead, action of, 33
- Leather-bottle stomach, 616
- Leiomyoma, appearance of, 209
 definition of, 209
 etiology of, 209
 nature of, 211
 of uterus, 784
 seats of, 210
 structure of, 210
- Leishmania donovani, 371
- Leishmaniosis, 370
- Lens of eye, 964
- Leontiasis leprosa, 328
 ossium, 845
- Lepra of bones, 853
 of larynx, 529
 of testicles, 822
- Leprosy, 147
 definition of, 326
 etiology of, 326
 of cornea, 972
 of liver, 672
 of nerves, 963
 of skin, 1003
 pathological anatomy of, 327, 328
- Leptomeningitis, 874
 acute, 930
 chronic, 878, 930
 purulent myelitis secondary to, 939
- Leptothrix buccalis, 324
- Lesser omental cavity, cystic accumulations in, 690
- Leucin in urine, 766
- Leukemia, acute, 441
 blood in, 440
 bone-marrow in, 464
 definition of, 438
 etiology of, 438
 lymphatic type of, 440
 myeloid type of, 440
 of lymphatic glands, 460
 of spleen, 449
 pathological anatomy of, 438
 stomatitis, 600
- Leukoblasts, 416
- Leukocytes, 414
 granules of, 417
 large mononuclear, 415
 number of, 418
 pathological changes in, 422
 polymorphonuclear, 415
 polynuclear, 415
 proportions of different forms of, 418
 rôle and fate of, in inflammation, 123
 transitional, 415
- Leukocytosis, 428
 cachectic, 429
 character of blood in, 429
- Leukocytosis, etiology of, 428
 from hemorrhage, 429
 from malignant tumors, 429
 infectious, 428
 inflammatory, 428
 mechanical and thermal causes of, 429
 medicinal, 429
 pathogenesis of, 429
 pathological physiology of, 430
- Leukopenia, 431
- Leukoplakia, 595
- Leukoprotease, 126
- Leukorrhea, 806
- Levulosuria, 759
- Leydenia gemmipara, 366
- Lichen, 999
- Linguatula rhinaria, 406
- Linitis gastrica, 616
- Lipaciduria, 761
- Lipemia, 425
- Lipoid metamorphoses, 85
- Lipoma, appearance of, 174
 definition of, 174
 etiology of, 174
 nature of, 175
 of bones, 853
 of Fallopian tubes, 802
 of kidneys, 741
 of mammary glands, 832
 of pancreas, 698
 of pia-arachnoid, 882
 of skin, 1005
 of vulva, 809
 seats of, 175
 structure of, 175
- Lipomatosis of mammary glands, 831
- Lipuria, 763
- Liquefaction necrosis, 109
 definition of, 109
 pathological anatomy of, 109
- Liquor puris, 133
- Lithopedia, 97, 804
- Liver, abscess of, 662
 acquired changes of form of, 653
 of position of, 654
 actinomycosis of, 672
 adenoma of, 674
 amyloid infiltration of, 661
 anatomical considerations of, 653
 anemia of, 654
 atrophy of, 657
 carcinoma of, 675
 cirrhosis of, 663
 congenital changes of position of, 653
 malformations of, 653
 cyanotic induration of, 655
 cysts of, 677
 dropsical infiltration of, 661
 fatty degeneration of, 659
 infiltration of, 658
 gin-drinkers', 665
 hob-nail, 665
 hyperemia of, 654
 hypertrophy of, 670
 leprosy of, 672
 lymphadenoma of, 674

Liver, parasites of, 677
 parenchymatous degeneration of, 659
 pigmentation of, 657
 red atrophy of, 655
 rupture of, 671
 sarcoma of, 674
 secondary carcinoma of, 676
 spots, 993
 syphilis of, 671
 tuberculosis of, 671
 Livores mortis, 116
 Local pigmentation, 102
 Locomotor ataxia, 944
 Ludwig's angina, 608
 Lungs, abscess of, 564
 actinomycosis of, 580
 active hyperemia of, 538
 anatomical considerations of, 537
 anemia of, 538
 atrophy of, 543
 carcinoma of, 581
 cavity formation in, 572
 congenital defects of, 538
 congestion of, 538
 cysts of, 584
 edema of, 540
 embolism of, 542
 emphysema of, 543
 gangrene of, 565
 glanders of, 579
 hemorrhage of, 540
 hemorrhagic infarcts of, 541
 hypertrophy of, 543
 inflammation of, 548
 parasites of, 584
 passive hyperemia of, 538
 sarcoma of, 580
 syphilis of, 578
 tuberculosis of, 566
 tumors of, 580
 Lupus, 1002
 erythematosus, 999
 verrucosa, 1003
 vulgaris, 321, 1003
 Luxation of joints, 855
 Lymphadenia ossea, 853
 Lymphadenitis, acute, 454
 chronic, 455
 suppurative, 455
 Lymphadenoma, appearance of, 185
 definition of, 184
 etiology of, 184
 nature of, 187
 of liver, 674
 of lymphatic glands, 461
 seats of, 185
 structure of, 186
 Lymphangiectasia, acquired, 522
 congenital, 522
 Lymphangioma, 181
 of brain, 921
 Lymphangitis, 521
 Lymphatic glands, 450
 anatomical considerations of, 450
 carcinoma of, 462
 endothelioma of, 462

Lymphatic glands, functions of, 451
 Hodgkin's disease of, 461
 leukemia of, 460
 lymphadenoma of, 461
 lymphoma of, 461
 lymphosarcoma of, 462
 sarcoma of, 462
 syphilis of, 459
 tuberculosis of, 456
 individual groups of, 458
 tumors of, 461
 tissues, diseases of, 443
 vessels, anatomical considerations of, 521
 dilatation of, 521
 inflammation of, 521
 parasites of, 523
 syphilis of, 522
 tuberculosis of, 522
 tumors of, 522
 Lymph-glands, amyloid infiltration of, 453
 atrophy of, 452
 calcification of, 453
 fatty infiltration of, 453
 hyaline degeneration of, 453
 inflammation of, 454
 necrosis of, 453
 pigmentation of, 454
 Lymphocytes, 414
 Lymphogenic tuberculosis, 577
 Lymphoma of lymphatic glands, 461
 Lymphoprotease, 126
 Lymphosarcoma, 194
 of lymphatic glands, 462
 Lyssophobia, 357
 MACROCEPHALY, 888
 Macrocheilia, 522, 594
 Macroglossia, 522, 594
 Macules, 995
 Malaria, parasites of, 372
 pathological anatomy of, 376
 physiology of, 376
 rôle of mosquitoes in, 375
 Malignant edema, definition of, 311
 etiology of, 311
 pathological anatomy of, 312
 physiology of, 312
 papilloma of mammary glands, 835
 pustule, 1001
 Mallein, 305
 Malta fever, definition of, 303
 etiology of, 303
 pathological anatomy of, 303
 physiology of, 303
 synonyms of, 303
 Mammary glands, abnormal development
 in male, 829
 functional activity of, 829
 adenocarcinoma of, 835
 adenoma of, 833
 atrophy of, 830
 carcinoma of, 833
 medullary, 834

- Mammary glands, carcinoma of, simple, 835
 squamous, 834
 chondroma of, 832
 cystadenoma of, 833
 cystosarcoma of, 833
 cysts of, 835
 early development of, 829
 fatty infiltration of, 831
 fibro-adenoma of, 831
 fibroma of, 831
 intracanalicular, 832
 hemorrhage from, 829
 hyperemia of, 829
 hypertrophy of, 830
 lipoma of, 832
 lipomatosis of, 831
 malignant papilloma of, 835
 myxoma of, 832
 myxomatous cancer of, 835
 degeneration of, 831
 osteoma of, 832
 Paget's disease of, 834
 pathological anatomy of, 830
 results of cancer of, 835
 sarcoma of, 833
 scirrhous cancer of, 834
 supernumerary, 828
 syphilis of, 831
 tuberculosis of, 831
 Marantic thrombi, 68
 Mast-cell granules, 417
 Mastigophora, 366
 Mastitis, acute, 829
 chronic, 830
 Maximow, polyblast of, 152
 Measles, 352
 Meckel's diverticulum, 626
 Medullary canal, 882
 folds, 882
 Megakaryocytes, 417
 Megaloblasts, 421
 Melostagmin reaction, 272
 Melanemia, 426
 Melanosarcoma, 197
 Melanosis, 974
 Melanuria, 761
 Melena neonatorum, 614
 Membrane, pyogenic, 134
 Mendel's law, 23
 Meningitis, epidemic cerebrospinal, 877
 other organisms in, 278
 tuberculous, 878
 Meningocele, 873, 888
 Meningococcus, distribution of, 278
 pathogenesis of, 278
 pathological physiology of, 278
 Menorrhagia, 63, 776
 Menstruation, 775
 Mercury, action of, 33
 Mesarteritis, 505
 Mesencephalon, 883
 Mesenteric arteries, embolism of, 632
 thrombosis of, 632
 Metabolic pigmentation, 104
 Metabolism, disorders of, 39
 Metabolism in diabetes, 51
 of fat, 40
 Metaplasia, 155
 Metastasis, 65, 167
 pigment, 102
 Metencephalon, 883
 Methemoglobin in urine, 766
 Metritis, 777
 acute, 780
 chronic, 780
 Metrorrhagia, 63, 776
 Miasmatic disease, 38
 Microblasts, 421
 Microcephaly, 889
 Micrococcus catarrhalis, 284
 gonorrhœa, 278
 melitensis, 303
 tetragenus, 284
 Micromyelia, 933
 Micro-organisms, entrance into body, 38
 Microphthalmia, 965
 Miliary tubercles, 319
 tuberculosis, 320
 Milium, 1007
 Mithridatization, 30
 Moles, hydatid, 813
 Molluscum contagiosum, 379, 1005
 appearances of, 380
 definition of, 379
 etiology of, 379
 seats of, 380
 structure of, 380
 Mononuclear leukocytes, large, 415
 Monsters, 239
 Morbid anatomy, definition of, 17
 physiology, definition of, 17
 Morgagni, hydatids of, 802
 Mosquitoes, rôle of, in malaria, 375
 in yellow fever, 351
 Mother wreath, 150
 Mouth, actinomycosis of, 600
 anemia of, 594
 hemorrhages of, 594
 syphilis of, 599
 tuberculosis of, 599
 tumors of, 600
 Mucoid degeneration, definition of, 88
 etiology of, 88
 microscopical appearances of, 89
 of bone-marrow, 464
 pathological anatomy of, 89
 physiology of, 90
 seats of, 89
 Mucopurulent cystitis, 754
 Mucous colitis, 639
 Mulberry calculi, 756
 Mummification, 112
 Mumps, 354
 Muscarin, 37
 Muscle tissue, regeneration of, 154
 Muscles, actinomycosis of, 869
 amyloid degeneration of, 868
 anemia of, 863
 anthrax of, 869
 atrophy of, 866
 calcification of, 868

- Muscles, coagulation necrosis of, 868
 embolism of arteries of, 863
 fatty degeneration of, 867
 infiltration of, 868
 glands of, 869
 hematoma of, 868
 hemorrhage in, 863
 hyaline degeneration of, 868
 hyperemia of, 863
 hypertrophy of, 863
 parasites of, 869
 parenchymatous degeneration of, 867,
 868
 syphilis of, 869
 thrombosis of veins of, 863
 tuberculosis of, 869
 tumors of, 869
 Mutation, 23
 Mycetoma, 346
 Mycobacterium influenzae, 298
 organisms resembling, 299
 leprae, 326
 tuberculosis, 313. See also *Bacillus*
 tuberculosis.
 Mycoses of skin, 1004
 Mycosis fungoides, 149, 199
 appearance of, 199
 associated conditions, 200
 etiology of, 199
 nature of, 200
 of external ear, 986
 structure of, 200
 Mydalein, 37
 Mydatoxin, 37
 Myelitis, hematogenous purulent, 939
 pressure-, 940
 secondary to purulent leptomeningitis,
 939
 transverse, secondary to injury or in-
 fectious disease, 939
 Myelocytes, 416
 Myeloid sarcoma, 195
 Myeloma, multiple, 188
 of bone-marrow, 466
 of bones, 854
 Myelomeningocele, 934
 Myeloplaxes, 417
 Myiasis, 406
 Myocarditis, acute, 487
 circumscribed, 487
 diffuse, 488
 chronic, 489
 Myocardium, 481. See also *Heart-*
 muscle.
 Myofibroma of uterus, 784
 of vagina, 807
 of vulva, 809
 Myoma of bladder, 758
 of mammary glands, 832
 Myopathic muscular atrophy, 867
 Myositis, chronic, 865
 productive, 865
 suppurative, 865
 disseminated acute, 864
 hemorrhagic, 864
 localized acute, 864
 Myositis ossificans progressiva, 865
 ossifying, 865
 serous, 864
 suppurative, 864
 Myotonia congenita, 867
 Myxedema, 706
 Myxoma, appearance of, 173
 definition of, 173
 etiology of, 173
 nature of, 174
 of bladder, 758
 of bones, 853
 of mammary glands, 832
 of testicles, 822
 seats of, 173
 structure of, 173
 Myxomatous degeneration of mammary
 glands, 831
 of testicles, 817
- NAILS, 1008
 inflammation of, 1008
 tumors of, 1008
 Nasal cavities, anatomical considerations
 of, 524
 congenital abnormalities of, 524
 edema of, 524
 foreign bodies in, 526
 hemorrhage of, 524
 hyperemia of, 524
 inflammation of, 525
 parasites of, 526
 syphilis of, 525
 tuberculosis of, 525
 tumors of, 526
 Necator americanus, 399
 Necrobiosis, 105
 Necroses, focal, 112
 Necrosis, 105
 circulatory derangements in, 106
 coagulation, 107
 definition of, 105
 etiology of, 105
 intoxications in, 106
 mechanical agents in, 106
 of bone-marrow, 464
 of bones, 846
 of lymph-glands, 453
 of pancreas, 686
 of skin, 993
 pressure-, of pharynx, 606
 trophic derangements in, 106
 Necrotic cells, altered karyokinesis in, 115
 inflammation, 137
 Nematodes, 395
 Nephritis, acute catarrhal, 722
 diffuse, 723
 hemorrhagic, 724
 parenchymatous, 722
 arteriosclerotic, 730, 736
 cardiac changes in, 736
 chronic, 726
 hemorrhagic, 726
 interstitial, 729
 primary, 730

- Nephritis, chronic interstitial, secondary,
 729
 parenchymatous, 726
 desquamative, 722
 edema in, 736
 embolic suppurative, 724
 etiology of, 720
 gouty, 730
 non-suppurative acute interstitial, 724
 pathological anatomy of, 721
 physiology of, 732
 secondary interstitial, 726
 senile, 737
 suppurative, 725
 tube-casts in, 733
 uremia in, 736
 urine in, 733, 735
 Nerve tissues, tumors from, 204
 Nerve-cells, 892
 functions of, 896
 Nerve-fibers, 897
 functions of, 897
 Nerve-poisons, poisoning from, 36
 Nerves, 958
 atrophy of, 959
 degeneration of, 959
 edema of, 958
 hemorrhage of, 958
 leprosy of, 963
 syphilis of, 963
 Nervous system, central, concussion of,
 917
 injuries to, 917
 general pathological anatomy of, 891
 influence of, in inflammation, 121
 sympathetic, 883
 tissue, regeneration of, 154
 Neurin, 37
 Neuritis, 960
 interstitial, acute, 961
 chronic, 962
 parenchymatous, 962
 Neuroblasts, 882
 Neuro-epithelioma, 207
 of brain, 920
 Neuroglia, degeneration of, 898
 Neuroglioma, ganglionar, of brain, 920
 Neuroma, appearance of, 208
 definition of, 208
 etiology of, 208
 nature of, 209
 of suprarenal bodies, 711
 seats of, 208
 structure of, 209
 Neuron, 885
 Neuropathic muscular atrophy, 866
 secondary, 867
 Neutrophiles, 415
 Neutrophilic granules, 418
 Nevus, 991
 New growths, autonomous, 159
 Nigrities, 598
 Nitrifying ferments, 248
 Noma, 597
 Non-contagious disease, 37
 Normoblasts, 421
 Nucleo-albuminuria, 762
 Nutmeg-liver, 655
 Nutrition, disorders of, 39
 in disease, 20
 OBESITAS cordis, 482
 Obesity, associated conditions, 41
 causes of, 40
 pathological anatomy of, 41
 Ochronosis, 760
 Odontomata of teeth, 602
 Oidiomycosis, 348
 Oidium albicans, 347
 Oligemia, 424
 Onychia, 1008
 Onychogryphosis, 1008
 Oöchronosis, 105
 Oöphoritis, 791
 chronic, 792
 Ophthalmitis, sympathetic, 980
 Opisthorchis felineus, 382
 sinensis, 382
 Opsonin theory of immunity, 258
 Optic nerve, atrophy of, 982
 inflammation of, 981
 syphilis of, 982
 tuberculosis of, 982
 tumors of, 982
 thalami, 883
 Orbit, 983
 tumors of, 983
 Orchitis, acute, 878
 chronic, 819
 Ossification, 98
 Osteatosis, 1007
 Osteo-arthritis, 859
 Osteo-arthropathy, hypertrophic, 843
 Osteoclasts, 845
 Osteogenesis imperfecta, 837
 Osteoma, appearance of, 179
 definition of, 179
 etiology of, 179
 nature of, 180, 181
 of bones, 853
 of brain, 922
 of mammary glands, 832
 of testicles, 822
 seats of, 180
 Osteomalacia, conditions associated with,
 849
 definition of, 848
 etiology of, 848
 pathological anatomy of, 848
 Osteomyelitis, 465
 conditions associated with, 844
 definition of, 843
 etiology of, 843
 pathological anatomy of, 844
 Osteoporosis, inflammatory, 845
 Osteopsathyrosis, 848
 Osteosarcoma, 195
 true, 196
 Osteosclerosis, 845
 Ostitis, 843
 chronic, 844

- Otitis, chronic, etiology of, 844
 pathological anatomy of, 845
 condensing, 845
 deformans, 846
 Otitis media, 987
 catarrhal, 988
 purulent, 988
 Ovaries, anatomical considerations of, 790
 carcinoma of, 796
 changes in position of, 790
 congenital abnormalities of, 790
 connective-tissue tumors of, 792
 cystomata of, 793
 dermoid cysts of, 795
 development of, 790
 follicular cysts of, 793
 hemorrhage from, 791
 hyperemia of, 791
 sarcoma of, 792
 tuberculosis of, 792
 Overfeeding, 40
 Oxalate of lime in urine, 764
 Oxaluria, 52
 Oxidizing ferments, 248
 Oxyphile granules, 417
 Oxyuris vermicularis, 396
 Ozena, 525

 PACCHIONIAN bodies, 880
 Pachydermia laryngis, 528
 Pachymeningitis adhesiva, 930
 cervicalis, 928
 external tuberculous, 928
 internal hemorrhagic, 870
 productive, 872
 suppurative external, 871
 Paget's disease of mammary glands, 834
 Pancreas, amyloid infiltration of, 686
 atrophy of, 685
 carcinoma of, 689, 698
 cirrhosis of, 688
 congenital abnormalities of, 685
 cysts of, 689
 fat-necrosis of, 686
 fibroma of, 698
 hemorrhage of, 685
 hyperemia of, 685
 inflammation of, 687. See also *Pan-*
 creatitis.
 lipoma of, 698
 necrosis of, 686
 parasites of, 698
 parenchymatous degeneration of, 685
 pigmentation of, 686
 sarcoma of, 689, 698
 syphilis of, 689
 tuberculosis of, 689
 Pancreatic acne, 690
 calculi, 690
 disease, pathological physiology of, 688
 duct, obstruction of, 690
 Pancreatitis, acute hemorrhagic, 687
 suppurative, 687
 chronic indurative, 688
 Pandemic disease, 38

 Pannus, 968
 Papillitis, 981
 Papillo-edema, 981
 Papilloma, appearance of, 212
 definition of, 212
 etiology of, 212
 nature of, 215
 of bladder, 757
 of larynx, 529
 of penis, 815
 of vagina, 807
 seats of, 213
 structure of, 214
 Papillomatous tumors of vulva, 809
 Papules, 995
 Paracolon infection, 294
 Paragonimus westermani, 383
 Parakeratosis, 998
 Paralbumin, 793
 Paralysis, general progressive, 916
 Landry's ascending, 943
 Paramecium coli, 379
 Parametritis, 777
 Parametrium, 803
 Paraphimosis, 814
 Parasites, animal, 38
 of blood, 442
 of bones, 854
 of bronchi, 537
 of intestines, 651
 animal, 652
 of kidneys, 751
 of larynx, 530
 of liver, 677
 of lungs, 584
 of lymphatic vessels, 523
 of malaria, 372
 of muscles, 869
 of nasal cavities, 526
 of pancreas, 698
 of pericardium, 502
 of pleura, 593
 of spleen, 450
 of thyroid gland, 705
 of uterus, 790
 vegetable, 37
 Parasitic diseases, 38
 Parathyroid glands, 707
 Paratyphoid fever, 646
 infection, 294
 intestinal lesions in, 295
 nature of, 295
 pathological anatomy of, 295
 Parenchymatous degeneration of heart,
 481
 of kidneys, 737
 of liver, 659
 of muscles, 867
 of pancreas, 685
 goiter, 700
 hepatitis, 662
 inflammation, 136
 Paresis, 916
 Parinaud's conjunctivitis, 968
 Paronychia, 1008
 Paroöphoron, 790

- Parotitis, 843
 Parotid gland, tumors of, 609
 Parovarium, 790
 cysts of, 796
 Pathological anatomy, definition of, 17
 chemistry, definition of, 17
 physiology, definition of, 17
 Pathology, definition of, 17
 general, 17
 special, 17
 Pearl disease, 143
 Pediculus vestimenti, 355
 Pellagra, 360
 Pemphigus, 996
 Penis, 814
 carcinoma of, 815
 chancroid of, 815
 concretions under prepuce of, 816
 condyloma acuminatum of, 815
 cysts of, 816
 epithelioma of, 815
 injuries of, 816
 papilloma of, 815
 secondary lesions of, 815
 syphilitic chancre of, 815
 tuberculosis of, 815
 Pentosuria, 52, 759
 Peptic ulcer, 134, 617
 Perforating ulcer, 134
 Perforation of esophagus, 611
 Periangiocholitis, 669
 Periappendiceal abscess, 638
 Peri-arteritis, 505
 nodosa, 507
 Peribronchitis, 534
 Pericarditis, 498
 acute, terminations of, 500
 conditions associated with, 502
 dry, 499
 fibrinous, 499
 hemorrhagic, 500
 purulent, 500
 serofibrinous, 500
 Pericardium, 498
 actinomycosis of, 502
 amyloid infiltration of, 504
 atrophy of, 504
 calcareous infiltration of, 504
 fatty degeneration of, 504
 hemorrhages of, 498
 hyaline degeneration of, 504
 hyperemia of, 498
 hypertrophy of, 503
 hypoplasia of, 503
 inflammation of, 498
 parasites in, 502
 syphilis of, 502
 tuberculosis of, 502
 tumors of, 502
 Perichondritis, 528, 595
 Perihepatitis, 670
 hyperplastic, 696
 Perimastitis, 830
 Perimetritis, 777
 Perinephric abscess, 725
 Periorchitis, 819
 Periorchitis prolifera, 820
 Periostitis, conditions associated with, 843
 definition of, 842
 etiology of, 842
 ossifying, 843
 pathological anatomy of, 842
 purulent, 842
 results of, 843
 simple, 842
 syphilitic, 852
 Periphlebitis, 518
 Periprostatitis, 824
 Perisplenitis, 450
 Perithelioma, 200
 of brain, 921
 Peritoneum, congenital abnormalities of, 691
 dropsy of, 692
 hemorrhage of, 691
 hyperemia of, 691
 inflammation of, 693. See also *Peritonitis*.
 tuberculosis of, 696
 Peritonitis, acute, effects of, 695
 general, 694
 localized, 694
 chronic, 695
 etiology of, 693
 Perityphlitis, 636
 Pernicious anemia, progressive, 435
 blood in, 436
 etiology of, 435
 pathogenesis of, 435
 pathological anatomy of, 436
 Pes calcaneus, 855
 equinus, 855
 valgus, 855
 varus, 855
 Petechiae, 62
 Pfeiffer's phenomenon, explanation of, 267
 Phagedenic ulcer, 134
 ulceration of cervix, 780
 Phagocytic cells, large mononuclear, in inflammation, 124
 Phagocytosis in inflammation, 123
 theory of immunity, 257
 Pharyngitis, catarrhal, 602
 chronic, 603
 phlegmonous, 603
 pseudomembranous, 603
 Pharyngomycosis leptothricia, 324, 607
 Pharynx, 602
 anemia of, 602
 diphtheria of, 606
 edema of, 602
 hemorrhages of, 602
 hyperemia of, 602
 pressure necrosis of, 606
 syphilis of, 607
 tuberculosis of, 607
 tumors of, 608
 Phimosis, 814
 Phlebectasia, 519
 Phlebitis, acute, 518

- Phlebitis, chronic, 518
 Phleboliths, 72, 518
 Phlebosclerosis, 518
 Phlegmon, 1002
 Phlegmonous cystitis, 754
 inflammation, 134
 pharyngitis, 603
 stomatitis, 596
 Phosphates in urine, 764
 Phosphaturia, 53
 Phosphorus, action of, 32
 metabolism of, 52
 Photogenesis of bacteria, 251
 Phthisis, acute caseous, 569
 chronic ulcerative, 569
 fibroid, 569, 573
 Physiology, morbid, 17
 pathological, 17
 Physometra, 775
 Pia-arachnoid, 873, 929
 anemia of, 874
 calcareous infiltration of, 929
 cholesteatoma of, 881
 edema of, 874
 endothelioma of, 880
 hemorrhage of, 929
 hyperemia of, 874, 929
 lipoma of, 882
 sarcoma of, 881
 syphilis of, 879, 930
 teratoma of, 882
 tuberculosis of, 930
 tumors of, 880, 931
 Pigment metastasis, 102
 Pigmentary cirrhosis, 670
 infiltration of choroid plexus, 923
 Pigmentation, 99
 from the exterior, 99
 hematogenous, 101
 hepatogenous, 104
 metabolic, 104
 of bone-marrow, 464
 of liver, 657
 of lymph-glands, 454
 of mucosa of intestines, 631
 of pancreas, 686
 of spleen, 448
 of stomach, 620
 of suprarenal bodies, 709
 Pineal gland, 715, 883
 Pinguecula, 969
 Pink-eye, 968
 Pituitary body, 712
 adenoma of, 714
 amyloid infiltration of, 714
 circulatory disturbances of, 713
 colloid degeneration of, 714
 cysts of, 714
 hypertrophy of, 713
 infectious diseases of, 714
 inflammation of, 713
 pathological physiology of, 714
 sarcoma of, 714
 Pityriasis versicolor, 1004
 Placenta, 810
 hyperplasia of, 812
 Placenta prævia, 810
 succenturiata, 810
 syphilis of, 812
 tuberculosis of, 812
 Placental infarcts, 811
 polypi, 813
 Placentitis, 811
 Plaques jaunes, 910
 Plasma cells, 416
 hyperinosis of, 424
 hypertonicity of, 424
 hypinosis of, 424
 of blood, 419
 pathological changes in, 423
 Plasmodia, parthenogenesis of, 374
 sporogony of, 374
 Plasmodium falciparum, 374
 malariae, 374
 vivax, 373
 Plethora, 424
 apocoptica, 424
 hydremica, 424
 vera, 424
 Pleura, 585
 anatomical considerations of, 585
 chronic thickening of, 590
 chylous effusion in, 586
 hyperemia of, 585
 inflammation of, 586. See also *Pleuritis*.
 parasites of, 593
 petechial hemorrhages of, 585
 syphilis of, 591
 tuberculosis of, 591
 tumors of, 592
 Pleurisy, 586. See also *Pleuritis*.
 Pleuritis, bread-and-butter, 588
 etiology of, 586
 fibrinous, 587
 hemorrhagic, 590
 lesions in other parts associated with, 590
 pathological anatomy of, 587
 physiology of, 591
 purulent, 589
 serofibrinous, 589
 tuberculous, 591
 Pleurogenic purulent pneumonia, 564
 Plexiform angiosarcoma, 201
 Pneumaturia, 761
 Pneumonia alba, 563
 aspiration, 554, 557
 bronchogenic, complications in, 574
 cheesy, 558. See also *Pneumonia, tuberculous*.
 classification of, 548
 congenital syphilitic, 563
 croupous, 280, 549. See also *Pneumonia, fibrinous*.
 deglutition, 554
 desiccans, 565
 fibrinous, 549, 550
 definition of, 549
 etiology of, 549
 lesions associated with, 552
 pathological anatomy of, 550

- Pneumonia, fibrinous, pathological physiology of, 552**
 stage of congestion or engorgement in, 550
 of consolidation or hepatization in, 550
 of resolution in, 551
 unusual characters of, 552
 terminations of, 553
fibrous, 560
 classification of, 560
 peribronchial, 562
 perivascular, 562
 pleurogenic, 562
 secondary, 562
hypostatic, 554, 557
 other forms of, 283
 organisms in, 284
pathological physiology of, 282
purulent, 563
 bronchogenic, 563
 hematogenic, 563
 pleurogenic, 564
tuberculous, 558
 etiology of, 558
 lesions associated with, 560
 pathological anatomy of, 558
 white, 563
Pneumonic tuberculosis, 569
Pneumonokoniosis, 99, 560
Pneumopericardium, 503
Pneumothorax, 586
Poikilocytosis, 420
Poisons, classification of, 31
 corrosive, action of, 31
 definition of, 29
 effect of, 30
 elimination of, 31
 fate of, after ingestion, 30
 general action of, 29
 in disease, 20
 in etiology of disease, 29
 organic, action of, 32
 parenchyma, action of, 32
Polio-encephalitis, 943
Poliomyelitis, 361
 acute anterior, 941
 chronic anterior, 951
 superior, 943
Polyblast of Maximow, 152
Polychromatophilia, 422
Polycoria, 974
Polycythemia, 427
 with chronic cyanosis and enlarged spleen, 428
Polymastia, 829
Polymorphonuclear leukocytes, 415
Polymyositis, 864
 secondary acute, 867
Polyneuritis, 962
Polynuclear leukocytes, 415
Polyorchism, 816
Polypi, 526, 811
 of uterus, 783
 placental, 813
Polypoid tumors of urethra, 770
- Polyuria, 759**
Pons, anatomy of, 884
Porencephaly, 890
Porocephalus constrictus, 406
Portal cirrhosis, changes associated with, 667
 morbid anatomy of, 666
 pathological physiology of, 668
 vein, embolism of, 656
 thrombosis of, 656
Posthitis, 814
Postmortem lividity, 57
Precipitin, 265
Pregnancy, abdominal, 805
 extra-uterine, 803
 interstitial, 803
 tubal, 803
Pressure, pathological effects of, 24
Pressure-myelitis, 940
Proctitis, 639
Productive inflammation, 137
Progressive muscular atrophy, 866
Prolapse of rectum, 630
 of uterus, 773
Proliferation cysts, 232
Proptosis, 983
Prosencephalon, 883
Prostate, 824
 abscess of, 824
 amylaceous bodies of, 825
 atrophy of, 824
 carcinoma of, 828
 concretions of, 825
 cysts of, 828
 fatty degeneration of, 825
 hypertrophy of, 825
 results of, 827
 sarcoma of, 827
 tuberculosis of, 825
Prostatitis, chronic, 824
 phlegmonous, 824
 simple, 824
 suppurative, 824
Protein metabolism, disorders of, 44
Proteins of bacteria, 247
Proteolytic ferments, 248
Proteus infection, 350
Prothrombin, 69
Protozoa, 364
Prurigo, 999
Psammoma, 97, 203, 204
 of brain, 922
Pseudoarthroses, 841
Pseudohermaphroditism, 814
Pseudohydrophobia, 357
Pseudohypertrophic muscular atrophy, 867
Pseudoleukemia, 441
 cutis, 200
 infantum, 441
Pseudomembranous cystitis, 754
 enteritis, 634
 gastritis, 614
 inflammation, 131, 287
 pharyngitis, 603
 stomatitis, 596

- Pseudomembranous vaginitis, 806
- Pseudomucin, 793
- Pseudotrichinosis, 864
- Pseudotuberculosis, 324
- Psoas abscess, 869
- Psoriasis, 998
- Pterygium, 969
- Ptomains, poisoning from, 36
- Ptoxis of eyelids, 983
- Puerperal infections, 780
 - etiology of, 780
 - pathological anatomy of, 780
- Pulmonary artery, stenosis and atresia of, 469
- Pulp of teeth, inflammation of, 601
- Purin metabolism, disorders of, 45
- Purulent pneumonia, 563
- Pustules, 135, 995
- Putrefaction, 248
- Pyelitis, 749
- Pyelonephritis, 750
 - suppurative, 725
- Pyemia, 253
- Pyknomorphous state, 893
- Pyogenic albumosuria, 761
 - membrane, 134
- Pyometra, 775
- Pyonephrosis, 750
- Pyopericardium, 500
- Pyopneumothorax, 586
- Pyorrhea alveolaris, 596
- Pyosalpinx, 801
- Pyothorax, purulent, 589

- QUINST, 605

- RABIES, 356
 - from bites, 357
 - microscopical anatomy of, 357
 - pathological anatomy of, 357
 - period of incubation in, 357
 - preventive inoculation for, 357
 - season for, 357
 - virus of, 356
- Race in disease, 20
- Rachischisis, 933
- Ranula, 601
- Reaction, meiostagmin, 272
- Rectocele, 773
 - vaginal, 805
- Rectum, inflammation of, 639
 - prolapse of, 630
- Red atrophy of liver, 655
 - corpuscles, 413
 - ameboid movements of, 421
 - basic degeneration of, 422
 - nucleated, 421
 - pathological changes in, 420
 - pigmentation of, 422
 - shape of, 420
 - size of, 420
 - skeined, 414
 - vacuolation of, 422
- Regeneration, definition of, 149
 - of adipose tissue, 154
 - of bone, 153
 - of cartilage, 153
 - of epithelium, 151
 - of fibrous connective tissue, 151
 - of glandular organs, 154
 - of muscle tissue, 154
 - of nervous tissue, 154
 - of skin, 993
 - pathological anatomy of, 150
 - physiology of, 155
- Relapsing fever, definition of, 339
 - etiology of, 339
 - pathological anatomy of, 340
 - physiology of, 340
- Renal sand, 749
- Repair of wounds, 137
- Reproductive organs, diseases of, 771
- Resolution after inflammation, 140
- Respiratory system, diseases of, 524
- Retention cysts, 232
- Retina, 965, 978
 - anemia of, 978
 - atrophy of, 978
 - detachment of, 979
 - glioma of, 206
 - hemorrhage of, 978
 - hyperemia of, 978
 - pigmentary degeneration of, 979
 - syphilis of, 980
 - tuberculosis of, 980
 - tumors of, 980
- Retinitis, albuminuric, 979
 - chronic, 979
 - diabetic, 979
 - pigmentosa, 979
 - purulent, 979
- Retroflexion of uterus, 773
- Retrograde change, 156
- Retrogressive processes, 76
- Retropharyngeal abscess, 603
- Retro-uterine hematocoele, 776
- Retroversion of uterus, 773
- Rhabdomyoma, appearance of, 212
 - definition of, 211
 - etiology of, 211
 - nature of, 212
 - of testicles, 822
 - seats of, 212
 - structure of, 212
- Rhachischisis, 888
- Rheumatism, 358
- Rhinitis, chronic, 525
 - diphtheritic, 525
- Rhinoliths, 526
- Rhinoscleroma, 148, 303
- Rhizopoda, 364
- Ribbert's theory of tumors, 160
- Ricin, poisoning from, 34
- Rickets, conditions associated with, 839
 - congenital, 837
 - definition of, 837
 - etiology of, 837
 - minute changes of, 838
 - pathological anatomy of, 838

- Rigor mortis, 115
 Ring abscess of cornea, 972
 bodies, 421
 Ringworm, 1004
 Rocky mountain fever, 362
 Rodent ulcer, 1006
 Round ulcer, 617
 Round-cell infiltration in inflammation, 127
 sarcoma, 193
 Round-worms, 395
 Rupture of intestines, 652
 of uterus, 775
 Russell's fuchsin bodies, 87
- SACCHAROMYCES hominis, 348
 Saccharomycosis, 148, 348
 Saccular aneurysm, 514
 Salivary ducts, diseases of, 609
 glands, inflammation of, 608. See also
 Parotitis.
 Salpingitis, acute, 799
 diphtheritic, 800
 chronic, 801
 Sappremia, 253
 Sarcoma, alveolar, 194
 appearances of, 189
 definition of, 189
 etiology of, 189
 giant-celled, 195
 myeloid, 195
 nature of, 191
 of bones, 853
 of brain, 920
 of dura mater, 929
 of Fallopian tubes, 802
 of intestines, 648
 of kidney, 743
 of liver, 674
 of lungs, 580
 of lymphatic glands, 462
 of mammary glands, 832
 of ovaries, 792
 of pancreas, 689, 698
 of pia-arachnoid, 881
 of pituitary body, 714
 of prostate, 827
 of skin, 1006
 of spinal cord, 957
 of spleen, 449
 of suprarenal bodies, 711
 of testicles, 822
 of thyroid gland, 705
 of urethra, 770
 of uterus, 785
 of vagina, 807
 of vulva, 809
 round-celled, 193
 seats of, 190
 spindle-celled, 193
 structure of, 190
 Sarcosporidia, 378
 Scabies, 1004
 Scales, skin, 995
 Scarlet fever, 353
- Schistosomum hæmatobium, 382
 japonicum, 383
 Schizomycetes, 242
 Sclera, 964, 972
 injury to, 973
 Sclerema, 992
 Scleritis, 972
 Scleroderma, 992
 Sclerosis of brain, atrophic, 899
 diffuse, 899
 disseminated, 899, 915
 hypertrophic nodular, 900
 lobar, 914
 multiple, 915
 of spinal cord, combined, 951
 lateral, 952
 amyotrophic, 949
 posterior, 944
 Scrofula, 322, 458
 Scrotum, 814
 elephantiasis of, 815
 Scutula, 1004
 Sebaceous cysts, 1007
 glands, 1006
 inflammation of, 1000
 tumors of, 1007
 Seborrhea, 1007
 Secondary carcinoma of liver, 676
 Segmentation, indirect, 150
 Sella turcica, 712
 Seminal vesicles, 828
 Septicemia, 253
 Sequestrum of bone, 846
 Serofibrinous pleuritis, 589
 Serous inflammation, 130
 Serpent venom, poisoning from, 34
 Serpiginous ulcer, 134
 Sex in disease, 20
 Siderosis, 100, 562
 Sinus thrombosis of dura mater, 870
 Sinuses, 134
 Skin, actinomycosis of, 1003
 anatomy of, 990
 anemia of, 993
 atrophy of, 991
 benign cystic epithelioma of, 1006
 circulatory disturbances of, 993
 congenital abnormalities of, 991
 crusts of, 995
 edema of, 994
 fibroma of, 1005
 glanders of, 1003
 hemorrhage into, 994
 hyperemia of, 994
 hypertrophy of, 991
 lenticular carcinoma of, 1006
 lipoma of, 1005
 mycoses of, 1004
 necrosis of, 993
 pigment of, 990
 regeneration of, 993
 sarcoma of, 1006
 scales of, 995
 specific inflammations of, 1002
 squamous epithelioma of, 1006
 syphilis of, 1003

- Skin, tuberculosis of, 1002.** See also *Lupus*.
 ulcers of, 1002
 variations in pigmentation of, 993
 xanthoma of, 1005
- Smegma bacillus, 324**
- Soft chancre, definition of, 302**
 etiology of, 302
 mixed infection in, 302
 pathological anatomy of, 302
 physiology of, 303
- Soil transmission of disease, 409**
- Specific inflammations, 141**
- Spermatocele, 823**
- Spider cells, 885**
- Spina bifida, 933**
- Spinal cord, anatomy of, 931**
 anemia of, 937
 carcinoma of, 957
 circulatory disturbances of, 936
 degenerations of, secondary, 953
 of white matter of, 952
 dilatation of central canal of, 933
 diseases of, 928
 double, 933
 hemorrhage of, 937
 heterotopia of gray matter of, 933
 hyaline degeneration of, 936
 hyperemia of, 937
 primary degenerations of, 943
 sarcoma of, 957
 sclerosis of, combined, 951
 lateral, 952
 amyotrophic, 949
 syphilis of, 943
 total absence of, 932
 tuberculosis of, 943
 unusual length of, 933
 varicose veins of, 937
 nerves, diseases of ganglia of, 958
- Spindle-celled sarcoma, 193**
- Spirilla, diseases due to, 330**
- Spirillaceæ, 242**
- Spirillum, 243**
 berlinense, 333
 cholerae asiaticæ, 330
 Metschnikovii, 333
 of Finkler and Prior, 333
 tyrogenicum, 333
 vincenti, 340
- Spirochæta carteri, 339**
 duttoni, 339
 novyi, 339
 obermeieri, 339
 pallida, 334
 pertenui, 341
- Spirochetes, diseases due to, 344**
- Splanchnoptosis, 621**
- Spleen, abnormal development of, 444**
 abscess of, 446
 amyloid infiltration of, 448
 anatomic considerations of, 443
 anemia of, 444, 447
 atrophy of, 448
 calcification of, 449
 carcinoma of, 449
- Spleen, chronic inflammation of, 447**
 circulatory disturbances of, 444
 cysts of, 449
 embolism of artery of, 445
 endothelioma of, 449
 enlarged, and chronic cyanosis, polycythemia with, 428
 hemorrhage in, 445
 Hodgkin's disease of, 449
 hyaline degeneration of, 448
 hyperemia of, 444
 inflammation of, 445
 leukemia of, 449
 malposition of, 444
 movable, 444
 parasites of, 450
 pathological physiology of, 443
 pigmentation of, 448
 sarcoma of, 449
 syphilis of, 450
 thrombosis of vein of, 445
 tuberculosis of, 450
- Splenic stones, 445**
- Splenitis, circumscribed, 446**
 diffuse, 445
 terminations of, 446
- Splenomegaly, 447**
- Spondylitis deformans, 859**
- Spongioblasts, 882**
- Sporothricosis, 149, 349**
- Sporothrix beurmanii, 349**
- Sporozoa in birds and cold-blooded animals, 376**
- Spring catarrh, 966**
- Spurious aneurysm, 517**
- Squamous epithelioma, 227**
- Staphylococcus group, 273**
 pyogenes albus, 275
 aureus, 273
 distribution of, 274
 pathogenicity of, 274
 pathological physiology of, 274
 citreus, 275
- Staphyloma, 970**
- Starvation, 39**
- Stasis of blood, 60**
- Status lymphaticus, 452, 712**
- Staubzellen, 560**
- Stimulation cells, 416**
- Stegomyia fasciata, 351**
- Stenosis of bile-ducts, 680**
 of bronchi, 534
 of esophagus, 610
 of Fallopian tubes, 798
 of intestines, 627
 of larynx, 529
 of uterus, 775
 of vagina, 805
- Stercoral typhlitis, 636**
- Stomach, alterations in position of, 621**
 amyloid infiltration of, 620
 anemia of, 613
 atrophy of glands of, 620
 calcification of, 620
 carcinoma of, 623
 congenital defects, 613

- Stomach, connective-tissue tumors of, 622**
 dilatation of, 621
 epithelial tumors of, 622
 fatty degeneration of, 620
 hemorrhage of, 613
 hyperemia of, 613
 infectious diseases of, 622
 inflammation of mucosa of, 614
 leather-bottle, 616
 pigmentation of, 620
Stomatitis, 594
 aphthous, 595
 catarrhal, 595
 conditions associated with, 598
 gangrenous, 597
 leukemic, 600
 parasitic, 598
 phlegmonous, 596
 pseudomembranous, 596
 ulcerative, 596
Strangulated hernia, 629
Strangulation of hernia, internal, 629
Streptococcus, distribution of, 276
 intracellularis meningitidis, 277
 pathogenesis of, 276
 pathological physiology of, 276
 pyogenes seu erysipclatis, 275
Streptothrix maduræ, 346
Stricture of urethra, 769
Strongyloides intestinalis, 400
Strongyloplasma hominis, 380
Strongylus apri, 405
 subtilis, 405
Struma, 700. See also Goiter.
 malignant, 705
Strumitis, 704
Stye, 983
Subcutis, inflammation of, 1001
Sudamina, 1008
Suffocation, 28
Suggillation, 63
Sulphates in urine, 766
Suppurative diseases, 273
 definition of, 273
 etiology of, 273
 inflammation, 132
 pancreatitis, acute, 687
Suprarenal bodies, accessory, 709
 adenoma of, 711
 amyloid infiltration of, 709
 anatomical considerations of, 708
 congenital anomalies of, 709
 fatty degeneration of, 709
 glioma of, 711
 hemorrhage of, 710
 hypernephroma of, 711
 inflammation of, 710
 neuroma of, 711
 pigmentation of, 709
 sarcoma of, 711
 syphilis of, 710
 tuberculosis of, 709
Sweat-glands, 1007
Swelling, cloudy, 78
Sycosis, 1000
Sylvius, aqueduct of, 884
Symblepharon, 969
Synceyrtoma malignum, 238
 of Fallopiian tubes, 802
Synceyrtum, 810
Synophthalmia, 965
Synovitis pannosa, 857
Syphilis, bubo of, 336
 chancre of, 146, 336
 condyloma latum of, 146
 congenital, 338
 definition of, 334
 etiology of, 334
 gumma of, 146
 histology of, 145
 mucous patch of, 146
 of arteries, 511
 of brain, 901
 of bladder, 753
 of bones, 851
 of brain, 919
 of bronchi, 536
 of cervix, 782
 of choroid, 978
 of ciliary body, 977
 of conjunctiva, 969
 of cornea, 972
 of dura mater, 872, 929
 of esophagus, 612
 of external ear, 986
 of Fallopiian tubes, 802
 of heart, 497
 of intestines, 647
 of iris, 975
 of joints, 861
 of kidneys, 741
 of larynx, 529
 of liver, 671
 of lungs, 578
 of lymphatic glands, 459
 vessels, 522
 of mammary glands, 831
 of middle ear, 988
 of mouth, 599
 of muscles, 869
 of nasal cavities, 525
 of nerves, 963
 of optic nerve, 982
 of pancreas, 689
 of pericardium, 502
 of pharynx, 607
 of pia-arachnoid, 879, 930
 of placenta, 812
 of pleura, 591
 of retina, 980
 of skin, 1003
 of spinal cord, 943
 of spleen, 450
 of suprarenal bodies, 710
 of testicles, 821
 of thymus gland, 712
 of thyroid, 705
 of trachea, 531
 of urethra, 770
 of vagina, 807
 of veins, 520
 of vulva, 809

- Syphilis, pathological anatomy of, 336
 physiology of, 338
 secondary lesions of, 336
 tertiary lesions of, 146, 337
 Syphilitic pneumonia, congenital, 563
 Syringomyelia, 935
- TABARDILLO, 355
 Tabes dorsalis, 944
 Tænia echinococcus, 390
 saginata, 388
 solium, 386
 adult, in man, 387
 geographical distribution of, 387
 larval state, in man, 386
 Tape-worms, 384
 pathological physiology of, 385
 Teeth, 601
 anomalous development of, 601
 caries of, 601
 Hutchinson's, 339, 601
 inflammation of pulp of, 601
 odontomata of, 602
 tumors of, 602
 Telangiectasis, simple angiomatous, 991
 Tendon-sheaths, ganglion of, 862
 inflammation of, 862
 Tenosynovitis, 862
 gonorrheal, 769
 Terata, 239
 Teratoid tumors, 236
 Teratology, 235
 Teratoma, definition of, 235
 etiology of, 236
 of pia-arachnoid, 882
 Testicles, adenoma of, 822
 adenosarcoma of, 822
 anatomical considerations of, 816
 atrophy of, 817
 benign fungus of, 819
 calcification of, 817
 carcinoma of, 822
 caseation of, 817
 chondrocarcinoma of, 822
 chondroma of, 822
 congenital abnormalities of, 816
 cysts of, 823
 dermoid cysts of, 823
 echinococcus cysts of, 824
 embolism of spermatic artery of, 818
 fatty degeneration of, 817
 fibroma of, 822
 hyperemia of, 818
 hypertrophy of, 817
 hypoplasia of, 816
 lepra of, 822
 myxoma of, 822
 myxomatous degeneration of, 817
 osteoma of, 822
 papilliferous cystoma of, 823
 physiological considerations of, 816
 rhabdomyoma of, 822
 sarcoma of, 822
 syphilis of, 821
 syphilitic fungus of, 822
- Testicles, tuberculosis of, 821
 Tetanolysin, 307
 Tetanospasmin, 307
 Tetanus, definition of, 306
 etiology of, 306
 pathological anatomy of, 307
 physiology of, 307
 Texas fever of cattle, 376
 Thalamencephalon, 883
 Thallophyta, 241
 Thelitis, 830
 Thoracic duct, diseases of, 523
 Thrombi, ball, 70
 Thrombin, 69
 Thrombo-angiitis, 506
 Thrombo-arteritis, 505
 Thrombophlebitis, 518
 Thrombosis, 67
 calcification after, 71
 canalization of, 72
 causes of, 67
 effects of, 70
 ferment, 68
 of bones, 841
 of brain, 908
 of cavities of heart, 471
 of coronary artery, 472
 of mesenteric arteries, 632
 of renal veins, 719
 of splenic vein, 445
 of veins of muscles, 863
 organization from, 72
 pathological anatomy of, 69
 subsequent changes in, 71
 Thrush, 347, 612
 Thymic asthma, 712
 Thymus gland, anatomy of, 711
 circulatory disturbances of, 712
 congenital abnormalities of, 711
 development of, 711
 inflammation of, 712
 syphilis of, 712
 tuberculosis of, 712
 tumors of, 712
 Thyroid disease, general results of, 706
 gland, abscess of, 700
 actinomycosis of, 705
 adenoma of, 705
 anatomical considerations of, 699
 circulatory disturbances in, 699
 congenital defects of, 699
 inflammation of, 700
 parasites of, 705
 sarcoma of, 705
 syphilis of, 705
 tuberculosis of, 705
 Thyroiditis, 700
 Tinea, 1004
 circinata, 1004
 sycosis, 1004
 tonsurans, 1004
 versicolor, 1004
 Tissue changes, progressive, 157
 destruction, excessive, 41
 Tongue, black, 598
 furring of, 595

- Tonsillitis, 604
 catarrhal, 604
 lacunar, 604
 pathological physiology of, 605
 phlegmonous, 605
 Tonsils, abscess of, 605
 hypertrophy of, 605
 Tophi, gouty, 46, 860
 Toxalbumins, 249
 from plants, poisoning from, 34
 Toxic enteritis, 633
 Toxin immunity, acquired, 260
 natural, 259
 Toxins of bacteria, 249
 Trachea, circulatory disturbances of, 531
 inflammation of, 531
 malformations of, acquired, 531
 congenital, 530
 syphilis of, 531
 tuberculosis of, 531
 tumors of, 531
 Trachoma, 362, 967
 Transitional leukocytes, 415
 Traumatic theory of carcinoma, 220
 Traumatism in etiology of disease, 24
 Trematodes, 380
 Treponema pallidum, 334
 Trichinella spiralis, 396
 Trichiniasis, 397
 Trichocephalus trichiurus, 401
 Trichomonas intestinalis, 367
 vaginalis, 368
 Trichorrhexis, 1008
 Trypanosoma, 369
 transmission of, 370
 Tubal abortion, 804
 pregnancy, 803
 Tube-casts, 733
 Tubercle, 995
 bacillus, 315. See also *Bacillus tuber-*
 culosis.
 foreign-body, 143
 structure and evolution of, 141
 Tuberculosis, 141
 bovine, 318
 bronchogenic, 567
 definition of, 313
 etiology of, 313
 fowl, 325
 hematogenic, 575
 latent, 322
 lymphogenic, 577
 miliary, 320
 of arteries, 511
 of bladder, 755
 of bones, 849
 of brain, 918
 of bronchi, 536
 of choroid, 978
 plexus, 923
 of ciliary body, 977
 of conjunctiva, 969
 of cornea, 972
 of dura mater, 872
 of esophagus, 612
 of external ear, 986
 Tuberculosis of Fallopian tubes, 801
 of heart, 497
 of intestines, 646
 of iris, 975
 of joints, 860
 of kidneys, 741, 750
 of larynx, 528
 of liver, 671
 of lungs, 566
 varieties of, 569
 of lymphatic glands, 456
 vessels, 522
 of mammary glands, 831
 of middle ear, 988
 of mouth, 599
 of muscles, 869
 of nasal cavities, 525
 of optic nerve, 982
 of ovaries, 792
 of pancreas, 689
 of penis, 815
 of pericardium, 502
 of peritoneum, 696
 of pharynx, 607
 of pia-arachnoid, 930
 of placenta, 812
 of pleura, 591
 of prostate, 825
 of retina, 980
 of skin, 1002
 of spinal cord, 943
 of spleen, 450
 of suprarenal bodies, 709
 of testicles, 821
 of thymus gland, 712
 of thyroid, 705
 of trachea, 531
 of urethra, 770
 of uterus, 782
 of vagina, 807
 of vas deferens, 821
 of veins, 520
 of vulva, 809
 pathological anatomy of, 319
 physiology of, 322
 pneumonic, acute, 569
 chronic, 570
 relation of human to animal, 318
 seats of, 321
 Tuberculous meningitis, 878
 pneumonia, 558
 Tubo-ovarian abscess, 792
 cysts, 802
 Tumors, benign, 167
 classification of, 168
 Cohnheim's theory of, 160
 connective-tissue, 169
 definition of, 158
 epithelial, 212
 etiology of, 159
 Hansemann's theory of, 161
 infectious character ascribed to, 161
 malignant, 167
 metastasis of, 167
 mixed, 198, 236
 number of, 165

- Tumors of biliary tract, 683**
 of bladder, 757
 of bones, 853
 of brain, 919
 of bronchi, 536
 of choroid, 978
 plexus, 923
 of ciliary body, 977
 of dura mater, 872, 929
 of esophagus, 612
 of external ear, 986
 of eye, 969
 of eyelids, 983
 of Fallopian tubes, 802
 of intestines, 648
 of iris, 976
 of joints, 862
 of kidneys, 741, 751
 secondary, 745
 of liver, 673
 of lungs, 580
 of lymphatic glands, 461
 vessels, 522
 of mammary glands, 831
 of middle ear, 989
 of mouth, 600
 of muscles, 869
 of nails, 1008
 of nasal cavities, 526
 of nerve tissues, 204
 of nerves, 963
 of optic nerve, 982
 of orbit, 983
 of ovaries, connective-tissue, 792
 cystic, 793
 of pancreas, 689
 of parotid gland, 609
 of penis, 815
 of pericardium, 502
 of peritoneum, 698
 of pharynx, 608
 of pia-arachnoid, 880, 931
 of pituitary body, 714
 of pleura, 592
 of prostate, 825
 of retina, 980
 of sebaceous glands, 1007
 of skin, 1005
 of spinal cord, 957
 of stomach, 622
 of suprarenal bodies, 711
 of teeth, 602
 of testicles, 822
 of thymus gland, 712
 of thyroid gland, 705
 of trachea, 531
 of urethra, 770
 of uterus, 784
 of vagina, 807
 of veins, 520
 of vulva, 809
 pathological physiology of, 166
 predisposing conditions, 163
 primary, 165
 Ribbert's theory of, 160
 secondary, 166
- Tumors, shape of, 165**
 structure of, 163
 synonyms of, 158
 teratoid, 236
 Virchow's theory of, 160
Tympanic membrane, 896
Typhilitis, 636
Typhoid fever, 642
 agglutination in, 292
 bacillus of, 289
 complications of, 645
 definition of, 289
 etiology of, 289
 Gruber-Durham phenomenon in, 292
 pathological anatomy of, 292
 physiology of, 292
 Widal reaction in, 293
 ulceration of esophagus, 612
Typhus fever, 355
Tyroma, 879
Tyrosin in urine, 766
Tyrotrocon, 36
- ULCER, 134**
 gastric, 617
 of bronchi, 534
 of skin, 1002
 peptic, 617
 round, 617
Ulcerative gastritis, 615
Umbilical cord, velamentous insertion of, 810
Uncinaria americana, 399
 duodenalis, 397
Unguis incarnatus, 1008
Urates in urine, 765
Uratc infiltration, 98
Uremia in nephritis, 736
Ureter, dilatation of, 748
 inflammation of, 750
 obstructions of, 748
Ureteritis, 750
Urethra, carcinoma of, 770
 congenital abnormalities of, 766
 cysts of, 770
 inflammation of, 767. See also *Urethritis*.
 injuries of, 770
 polypoid tumors of, 770
 sarcoma of, 770
 stricture of, 769
 syphilis of, 770
 tuberculosis of, 770
Urethritis, 767
 anterior, 768
 gonorrheal, 770
 lesions associated with, 767
 pathological anatomy of, 767
 posterior, 768
 specific, 767
Uric acid in urine, 764
Urinary organs, diseases of, 717
Urine, abnormal conditions of, 758
 bilirubin in, 766

- Urine, carbonates in, 766
 chemical changes in, 764
 cholesterin in, 766
 color of, 759
 cystin in, 766
 fat crystals in, 766
 hematinoid in, 766
 hemoglobin in, 766
 hippuric acid in, 765
 in nephritis, 733, 735
 indigo in, 766
 leucin in, 766
 methemoglobin in, 766
 oxalate of lime in, 764
 phosphates in, 764
 quantity of, 758
 reaction of, 759
 sediments in, 764
 specific gravity of, 759
 sulphates in, 766
 tyrosin in, 766
 urates in, 765
 uric acid in, 764
 xanthin in, 766
- Urinerous tubules, concretions in, 740
- Urobilinuria, 760
- Urticaria, 994
- Uterus, adenofibroma of, 785
 adenoma of, 787
 adenomyoma of, 785
 anatomy of, 771
 antelexion of, 772
 anteversion of, 772
 bicornis, 771
 carcinoma of, 788
 congenital abnormalities of, 771
 cysts of, 790
 development of, 771
 dilatation of, 775
 duplexus, 772
 erosions of, 779
 fatty degeneration of, 783
 fibroids of, 784
 hemorrhage from, 776
 hyperemia of, 775
 hyperplasia of mucous membrane of, 783
 hypertrophy of, 783
 infantilis, 771
 infectious diseases of, 780
 inversion of, 773
 lateral displacements of, 773
 leiomyoma of, 784
 myofibroma of, 784
 parasites of, 790
 polypt, 783
 prolapse of, 773
 puerperal atrophy of, 783
 retroflexion of, 773
 retroversion of, 773
 rupture of, 775
 sarcoma of, 785
 senile atrophy of, 783
 septus, 771
 stenosis of, 775
 tuberculosis of, 782
- Uterus unicornis, 772
 upward dislocation of, 773
- Uveal tract, hyperemia of, 975
- VACCINIA, 354
- Vacuolization, 894
- Vagina, carcinoma of, 807
 cysts of, 807
 fibroma of, 807
 hemorrhage into walls of, 806
 hyperemia of, 806
 myofibroma of, 807
 papilloma of, 807
 prolapse of walls of, 805
 sarcoma of, 807
 stenosis of, 805
 syphilis of, 807
 tuberculosis of, 807
- Vaginal cystocele, 805
 rectocele, 805
- Vaginitis, aphthous, 806
 chronic catarrhal, 806
 emphysematous, 806
 erysipeloid, 806
 exfoliative, 806
 pseudomembranous, 806
 senile, 806
 testis, 818, 819
 hemorrhagic, 820
 purulent, 820
 serous, 819
- Varicella, 355, 996
- Varicocele, 820
- Varicose veins of spinal cord, 937
- Varicosity, 519
- Variola, 354, 966
- Vas deferens, inflammation of, 820
 tuberculosis of, 821
- Vasomotor disturbances, 57
- Veins, 517
 anatomical considerations of, 517
 calcification of, 518
 circulatory disturbances of, 517
 dilatation of, 519
 fatty degeneration of, 518
 syphilis of, 520
 tuberculosis of, 520
 tumors of, 520
- Venereal wart, 212
- Ventricles, ependymitis of, 923
- Ventricular septum, defects of, 469
- Vermes, 380
- Verruca, 992
- Vesicles, 995
- Vibrio cholerae asiatica, 330
 organisms resembling, 333
- Vincent's angina, 340, 607
- Virchow's theory of inflammation, 118
 of tumors, 160
- Virus of rabies, 356
- Viruses, filterable, 351
- Vitiligo, 993
- Vitreous humor, 965
 chemical changes in, 974
 hemorrhage into, 974

Vitreous humor, inflammation of, 974
Volvulus of intestines, 629
Vulva, 807
 abscess of, 808
 adenoma of, 809
 carcinoma of, 809
 caruncle of, 809
 chancroids of, 809
 cysts of, 809
 diphtheria of, 809
 edema of, 808
 elephantiasis of, 809
 fibroma of, 809
 fibromyxoma of, 809
 gangrene of, 809
 hematoma of, 808
 hyperemia of, 808
 inflammation of, acute catarrhal, 808
 chronic, 808
 phlegmonous, 808
 lipoma of, 809
 myofibroma of, 809
 papillomatous tumors of, 809
 sarcoma of, 809
 syphilis of, 809
 tuberculosis of, 809
 wounds of, 808

WARTS, 992
 venereal, 212

Water transmission of disease, 409
Wen, 991, 1007
White corpuscles, 414
Whooping-cough, Bordet-Gengou bacillus of, 299
Widal reaction in typhoid fever, 292
Wine stain, 991
Wounds of cornea, 972
 repair of, 137
 tissue changes from, 24

XANTHIN in urine, 766
Xanthoma, definition of, 175
 nature of, 176
 of skin, 1005
 structure of, 175
Xerosis, 969
X-ray in etiology of disease, 29

YAWS, 341
Yellow atrophy of liver, acute, 659
 fever, definition of, 351
 etiology of, 351
 pathological anatomy of, 352
 physiology of, 352
 rôle of mosquitoes in, 351

ZUCKERGUSSLEBER, 670, 696

SAUNDERS' BOOKS

on

**Pathology, Physiology
Histology, Embryology
Bacteriology, Biology**

W. B. SAUNDERS COMPANY
WEST WASHINGTON SQUARE PHILADELPHIA
9, HENRIETTA STREET COVENT GARDEN, LONDON

Prentiss' Embryology

Laboratory Manual and Text-Book of Embryology. By CHARLES W. PRENTISS, PH. D., Professor of Microscopic Anatomy, Northwestern University Medical School, Chicago. Large octavo of 400 pages, with 368 illustrations, 50 in colors. Cloth, \$3.75 net.

JUST ISSUED

Prof. Prentiss' new work has many features that make it extremely valuable to students and teachers of vertebrate or human embryology. It is the only recent single volume describing *the chick and pig embryos* usually studied in the laboratory; and at the same time it gives a concise, systematic account of human embryology. The descriptions of the embryos to be studied in the laboratory are concise, yet they are profusely illustrated, the majority of the pictures being original.

It is the only comparatively brief text in which a large number of original dissections of pig and human embryos are described and illustrated, and in which directions are given for making dissections of the nervous system, viscera, face, palate, and tongue of these embryos. Of the same embryos from which series of transverse sections have been made, illustrations are given, showing the external form and internal structure. The student will thus be enabled to determine the position and plane of section of each section studied. There are, in addition, original illustrations of the development of the heart, urogenital organs, and nervous system. The book contains 368 illustrations, 50 in colors.

Mallory's Pathologic Histology

Pathologic Histology. By FRANK B. MALLORY, M. D., Associate Professor of Pathology, Harvard University Medical School. Octavo of 677 pages, with 497 figures containing 683 original illustrations, 124 in colors. Cloth, \$5.50 net; Half Morocco, \$7.00 net.

REPRINTED IN THREE MONTHS

Dr. Mallory here presents *pathology* from the morphologic point of view. He presents his subject biologically, first by ascertaining the cellular elements out of which the various lesions are built up; then he traces the development of the lesions from the simplest to the most complex. He so presents pathology that you are able to trace backward from any given end-result, such as sclerosis of an organ (cirrhosis of the liver, for example), through all the various acute lesions that may terminate in that particular end-result to the primal *cause* of the lesion. The *illustrations* are most beautiful.

Dr. W. G. MacCallum, *Columbia University*

"I have looked over the book and think the plan is admirably carried out and that the book supplies a need we have felt very much. I shall be very glad to recommend it."

Howell's Physiology

A Text-Book of Physiology. By WILLIAM H. HOWELL, PH.D., M. D., Professor of Physiology in the Johns Hopkins University, Baltimore, Md. Octavo of 1020 pages, 306 illustrations. Cloth, \$4.00 net.

THE NEW (5th) EDITION

Dr. Howell has had many years of experience as a teacher of physiology in several of the leading medical schools, and is therefore exceedingly well fitted to write a text-book on this subject. Main emphasis has been laid upon those facts and views which will be directly helpful in the practical branches of medicine. At the same time, however, sufficient consideration has been given to the experimental side of the science. The entire literature of physiology has been thoroughly digested by Dr. Howell, and the important views and conclusions introduced into his work. Illustrations have been most freely used.

The Lancet, London

"This is one of the best recent text-books on physiology, and we warmly commend it to the attention of students who desire to obtain by reading a general, all-round, yet concise survey of the scope, facts, theories, and speculations that make up its subject matter."

Mallory and Wright's Pathologic Technique

Just Ready—New (6th) Edition

Pathologic Technique. A Practical Manual for Workers in Pathologic Histology, including Directions for the Performance of Autopsies and for Clinical Diagnosis by Laboratory Methods. By FRANK B. MALLORY, M. D., Associate Professor of Pathology, Harvard University; and JAMES H. WRIGHT, M. D., Pathologist to the Massachusetts General Hospital. Octavo of 536 pages, with 174 illustrations. Cloth, \$3.00 net.

In revising the book for the new edition the authors have kept in view the needs of the laboratory worker, whether student, practitioner, or pathologist, for a practical manual of histologic and bacteriologic methods in the study of pathologic material. Many parts have been rewritten, many new methods have been added, and the number of illustrations has been considerably increased.

Boston Medical and Surgical Journal

"This manual, since its first appearance, has been recognized as the standard guide in pathologic technique, and has become well-nigh indispensable to the laboratory worker."

Eyre's Bacteriologic Technic

Bacteriologic Technic. A Laboratory Guide for the Medical, Dental, and Technical Student. By J. W. H. EYRE, M. D., F. R. S. Edin., Director of the Bacteriologic Department of Guy's Hospital, London. Octavo of 520 pages, 219 illustrations. Cloth, \$3.00 net.

NEW (2d) EDITION, REWRITTEN

Dr. Eyre has subjected his work to a most searching revision. Indeed, so thorough was his revision that the entire book, enlarged by some 150 pages and 50 illustrations, had to be reset from cover to cover. He has included all the latest technic in every division of the subject. His thoroughness, his accuracy, his attention to detail make his work an important one. He gives clearly the technic for the bacteriologic examination of water, sewage, air, soil, milk and its products, meats, etc. And he gives you good technic—methods attested by his own large experience. To any one interested in this line of endeavor the new edition of Dr. Eyre's work is indispensable. The illustrations are as practical as the text.

McFarland's Pathology

A Text-Book of Pathology. By JOSEPH MCFARLAND, M. D., Professor of Pathology and Bacteriology in the Medico-Chirurgical College of Philadelphia. Octavo of 856 pages, with 437 illustrations, many in colors. Cloth, \$5.00 net; Half Morocco, \$6.50 net.

THE NEW (2d) EDITION

You cannot successfully treat disease unless you have a practical, *clinical* knowledge of the pathologic changes produced by disease. For this purpose Dr. McFarland's work is well fitted. It was written with just such an end in view—to furnish a ready means of acquiring a thorough training in the subject, a training such as would be of daily help in your practice. For this edition every page has been gone over most carefully, correcting, omitting the obsolete, and adding the new. Some sections have been entirely rewritten. You will find it a book well worth consulting, for it is the work of an authority.

St. Paul Medical Journal

"It is safe to say that there are few who are better qualified to give a résumé of the modern views on this subject than McFarland. The subject-matter is thoroughly up to date."

Boston Medical and Surgical Journal

"It contains a great mass of well-classified facts. One of the best sections is that on the special pathology of the blood."

McFarland's

Biology: Medical and General

Biology: Medical and General.—By JOSEPH MCFARLAND, M. D., Professor of Pathology and Bacteriology in the Medico-Chirurgical College of Phila. 12mo, 457 pages, 160 illustrations. Cloth, \$1.75 net.

NEW (2d) EDITION

This work is both a *general* and *medical* biology. The former because it discusses the peculiar nature and reactions of living substance generally; the latter because particular emphasis is laid on those subjects of special interest and value in the study and practice of medicine. The illustrations will be found of great assistance.

Frederic P. Gorham, A. M., Brown University.

"I am greatly pleased with it. Perhaps the highest praise which I can give the book is to say that it more nearly approaches the course I am now giving in general biology than any other work."

McFarland's Pathogenic Bacteria and Protozoa

Pathogenic Bacteria and Protozoa. By JOSEPH MCFARLAND, M. D., Professor of Pathology and Bacteriology in the Medico-Chirurgical College of Philadelphia. Octavo of 878 pages, finely illustrated. Cloth, \$3.50 net.

NEW (7th) EDITION, ENLARGED

Dr. McFarland has subjected his book to a most vigorous revision, bringing this edition right down to the minute. Important new additions have increased it in size some 180 pages, By far the most important addition is the inclusion of an entirely new section on *Pathogenic Protozoa*. This section considers every protozoan pathogenic to man; and in that same clean-cut, definite way that won for McFarland's work a place in the very front of medical bacteriologies. The illustrations are the best the world affords, and are beautifully executed.

H. B. Anderson, M. D.,

Professor of Pathology and Bacteriology, Trinity Medical College, Toronto.

"The book is a satisfactory one, and I shall take pleasure in recommending it to the students of Trinity College."

The Lancet, London

"It is excellently adapted for the medical students and practitioners for whom it is avowedly written. . . . The descriptions given are accurate and readable."

Hill's Histology and Organography

A Manual of Histology and Organography. By CHARLES HILL, M. D., formerly Assistant Professor of Histology and Embryology, Northwestern University, Chicago. 12mo of 483 pages, 337 illustrations. Cloth, \$2.25 net.

THE NEW (3d) EDITION

Dr. Hill's work is characterized by a completeness of discussion rarely met in a book of this size. Particular consideration is given the mouth and teeth.

Pennsylvania Medical Journal

"It is arranged in such a manner as to be easy of access and comprehension. To any contemplating the study of histology and organography we would commend this work."

GET
THE BEST

American Illustrated Dictionary

THE NEW
STANDARD

New (7th) Edition—5000 Sold in Two Months

The American Illustrated Medical Dictionary. A new and complete dictionary of the terms used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Veterinary Science, Nursing, and kindred branches; with over 100 new and elaborate tables and many handsome illustrations. By W. A. NEWMAN DORLAND, M.D., Editor of "The American Pocket Medical Dictionary." Large octavo, 1107 pages, bound in full flexible leather. Price, \$4.50 net; with thumb index, \$5.00 net.

IT DEFINES ALL THE NEW WORDS—IT IS UP TO DATE

The American Illustrated Medical Dictionary defines hundreds of the newest terms not defined in any other dictionary—bar none. These new terms are live, active words, taken right from modern medical literature.

It gives the capitalization and pronunciation of all words. It makes a feature of the derivation or etymology of the words. In some dictionaries the etymology occupies only a secondary place, in many cases no derivation being given at all. In the American Illustrated practically every word is given its derivation.

Every word has a separate paragraph, thus making it easy to find a word quickly.

The tables of arteries, muscles, nerves, veins, etc., are of the greatest help in assembling anatomic facts. In them are classified for quick study all the necessary information about the various structures.

Every word is given its definition—a definition that *defines* in the fewest possible words. In some dictionaries hundreds of words are not defined at all, referring the reader to some other source for the information he wants at once.

Howard A. Kelly, M. D., *Johns Hopkins University, Baltimore.*

"The American Illustrated Dictionary is admirable. It is so well gotten up and of such convenient size. No errors have been found in my use of it."

J. Collins Warren, M. D., LL.D., F.R.C.S. (Hon.), *Harvard Medical School*

"I regard it as a valuable aid to my medical literary work. It is very complete and of convenient size to handle comfortably. I use it in preference to any other."

Stengel's Pathology

A Text-Book of Pathology. By ALFRED STENGEL, M. D., Professor of Medicine in the University of Pennsylvania. Octavo volume of 979 pages, with 400 text-illustrations, many in colors, and 7 full-page colored plates. Cloth, \$5.00 net; Sheep or Half Morocco, \$6.50 net.

FIFTH EDITION, WITH 400 ILLUSTRATIONS

In this work the practical application of pathologic facts to clinical medicine is considered more fully than is customary in works on pathology. While the subject is treated in the broadest way consistent with the size of the book, an effort has been made to present the subject from the point of view of the clinician.

"This volume is intended to present the subject of pathology in as practical a form as possible, and more especially from the point of view of the 'clinical pathologist.' These objects have been faithfully carried out, and a valuable text-book is the result. We can most favorably recommend it to our readers as a thoroughly practical work on clinical pathology."—*The Lancet, London.*

Stiles on the Nervous System

The Nervous System and its Conservation. By PERCY G. STILES, Instructor in Physiology at Harvard University. 12mo of 230 pages, illustrated. Cloth, \$1.25 net.

ILLUSTRATED

You get chapters on the minute structure, elements of nerve physiology, reflexes, anatomy, afferent nervous system, neuromuscular system and fatigue, autonomic system, the cerebrum and human development, emotion, sleep, dreams, causes of nervous impairment, neurasthenia, hygiene.

Stiles' Nutritional Physiology

Nutritional Physiology. By PERCY GOLDTHWAIT STILES, Instructor in Physiology at Harvard University. 12mo of 295 pages, illustrated. Cloth, \$1.25 net.

ILLUSTRATED

This new work expresses the most advanced views on this important subject. It discusses in a concise way the processes of digestion and metabolism. The key-word of the book throughout is "energy"—its source and its conservation.

"It is remarkable for the fineness of its diction and for its clear presentation of the subject, relieved here and there by a quaintly humorous turn of phrase that is altogether delightful."—*Colin C. Stewart, Ph. D., Dartmouth College.*

Jordan's General Bacteriology

A Text-Book of General Bacteriology. By EDWIN O. JORDAN, Ph.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Octavo of 650 pages, illustrated. Cloth, \$3.00 net.

NEW (4th) EDITION

Professor Jordan's work embraces the entire field of bacteriology, the non-pathogenic as well as the pathogenic bacteria being considered, giving greater emphasis, of course, to the latter. There are extensive chapters on methods of studying bacteria, including staining, biochemical tests, cultures, etc.; on the development and composition of bacteria; on enzymes and fermentation-products; on the bacterial production of pigment, acid and alkali; and on ptomaines and toxins. Especially complete is the presentation of the serum treatment of gonorrhea, diphtheria, dysentery, and tetanus. The relation of bovine to human tuberculosis and the ocular tuberculin reaction receive extensive consideration.

This work will also appeal to academic and scientific students. It contains chapters on the bacteriology of plants, milk and milk-products, air, agriculture, water, food preservatives, the processes of leather tanning, tobacco curing, and vinegar making; the relation of bacteriology to household administration and to sanitary engineering, etc.

Prof. Severance Burrage, *Associate Professor of Sanitary Science, Purdue University.*

"I am much impressed with the completeness and accuracy of the book. It certainly covers the ground more completely than any other American book that I have seen."

Buchanan's Veterinary Bacteriology

Veterinary Bacteriology. By ROBERT E. BUCHANAN, Ph.D., Professor of Bacteriology in the Iowa State College of Agriculture and Mechanic Arts. Octavo, 516 pages, 214 illustrations. Cloth, \$3.00 net.

THE BEST PUBLISHED

Professor Buchanan discusses thoroughly all bacteria causing diseases of the domestic animals. He goes minutely into the consideration of immunity, opsonic index, reproduction, sterilization, antiseptics, biochemic tests, culture-media, isolation of cultures, the manufacture of the various toxins, antitoxins, tuberculins, and vaccines that have proved of diagnostic or therapeutic value. Then, in addition to bacteria and protozoa proper, he considers molds, mildews, smuts, rusts, toadstools, puff-balls, and the other fungi pathogenic for animals.

B. F. Kaupp, D. V. S., *State Agricultural College, Fort Collins.*

"It is the best in print on the subject. What pleases me most is that it contains all the late results of research. It fills a long felt want."

Heisler's Embryology

A Text-Book of Embryology. By JOHN C. HEISLER, M. D., Professor of Anatomy in the Medico-Chirurgical College, Philadelphia. Octavo volume of 435 pages, with 212 illustrations, 32 of them in colors. Cloth, \$3.00 net.

THIRD EDITION—WITH 212 ILLUSTRATIONS, 32 IN COLORS

This edition represents all the advances recently made in the science of embryology. Many portions have been entirely rewritten, and a great deal of new and important matter added. A number of new illustrations have also been introduced and these will prove very valuable. Heisler's Embryology has become a standard work.

G. Carl Huber, M. D.,

Professor of Embryology at the Wistar Institute, University of Pennsylvania.

"I find this edition of 'A Text-Book of Embryology,' by Dr. Heisler, an improvement on the former one. The figures added increase greatly the value of the work. I am again recommending it to our students."

Böhm, Davidoff, and Huber's Histology

A Text-Book of Human Histology. Including Microscopic Technic. By DR. A. A. BÖHM and Dr. M. VON DAVIDOFF, of Munich, and G. CARL HUBER, M. D., Professor of Embryology at the Wistar Institute, University of Pennsylvania. Handsome octavo of 528 pages, with 361 beautiful original illustrations. Flexible cloth, \$3.50 net.

SECOND EDITION, ENLARGED

The work of Drs. Böhm and Davidoff is well known in the German edition, and has been considered one of the most practically useful books on the subject of Human Histology. This second edition has been in great part rewritten and very much enlarged by Dr. Huber, who has also added over one hundred original illustrations. Dr. Huber's extensive additions have rendered the work the most complete students' text-book on Histology in existence.

Boston Medical and Surgical Journal

"Is unquestionably a text-book of the first rank, having been carefully written by thorough masters of the subject, and in certain directions it is much superior to any other histological manual."

Wells' Chemical Pathology

Chemical Pathology.—Being a Discussion of General Pathology from the Standpoint of the Chemical Processes Involved. By H. GIDEON WELLS, PH. D., M. D., Assistant Professor of Pathology in the University of Chicago. Octavo of 616 pages. Cloth, \$3.25 net.

NEW (2d) EDITION

Dr. Wells' work is written for the physician, for those engaged in research in pathology and physiologic chemistry, and for the medical student. In the introductory chapter are discussed the chemistry and physics of the animal cell, giving the essential facts of ionization, diffusion, osmotic pressure, etc., and the relation of these facts to cellular activities. Special chapters are devoted to *Diabetes* and to *Uric-acid Metabolism and Gout*.

Wm. H. Welch, M. D.

Professor of Pathology, Johns Hopkins University.

"The work fills a real need in the English literature of a very important subject, and I shall be glad to recommend it to my students."

Lusk's Elements of Nutrition

Elements of the Science of Nutrition. By GRAHAM LUSK, PH. D., Professor of Physiology at Cornell Medical School. Octavo volume of 302 pages. Cloth, \$3.00 net.

THE NEW (2d) EDITION—TRANSLATED INTO GERMAN

Prof. Lusk presents the scientific foundations upon which rests our knowledge of nutrition and metabolism, both in health and in disease. There are special chapters on the metabolism of diabetes and fever, and on purin metabolism. The work will also prove valuable to students of *animal dietetics* at agricultural stations.

Lewellys F. Barker, M. D.

Professor of the Principles and Practice of Medicine, Johns Hopkins University.

"I shall recommend it highly to my students. It is a comfort to have such a discussion of the subject in English."

Daugherty's Economic Zoölogy

Economic Zoölogy. By L. S. DAUGHERTY, M. S., Ph. D., Professor of Zoölogy, State Normal School, Kirksville, Mo., and M. C. DAUGHERTY, author with Jackson of "Agriculture Through the Laboratory and School Garden." Part I: *Field and Laboratory Guide*. 12mo of 237 pages, interleaved. Cloth, \$1.25 net. Part II: *Principles*. 12mo of 406 pages, illustrated. Cloth, \$2.00 net.

ILLUSTRATED

There is no other book just like this. Not only does it give the salient facts of structural zoölogy and the development of the various branches of animals, but also the natural history—the *life and habits*—thus showing the interrelations of structure, habit, and environment. In a word, it gives the principles of zoölogy and *their actual application*. The economic phase is emphasized. Part I—the *Field and Laboratory Guide*—is designed for practical instruction in the field and laboratory. To enhance its value for this purpose blank pages are inserted for notes.

Drew's Invertebrate Zoölogy

A Laboratory Manual of Invertebrate Zoology. By GILMAN A. DREW, Ph. D., Assistant Director at Marine Biological Laboratory, Woods Hole, Mass. With the aid of Former and Present Members of the Zoölogical Staff of Instructors. 12mo of 213 pages. Cloth, \$1.25 net.

NEW (2d) EDITION

The subject is presented in a logical way, and the type method of study has been followed, as this method has been the prevailing one for many years.

Prof. Allison A. Smyth, Jr., Virginia Polytechnic Institute

"I think it is the best laboratory manual of zoölogy I have yet seen. The large number of forms dealt with makes the work applicable to almost any locality."

Norris' Cardiac Pathology

Studies in Cardiac Pathology. By GEORGE W. NORRIS, M.D., Associate in Medicine at the University of Pennsylvania. Large octavo of 235 pages, with 85 superb illustrations. Cloth, \$5.00 net.

SUPERB ILLUSTRATIONS

The illustrations are superb. Each illustration is accompanied by a detailed description; besides, there is ample letter press supplementing the pictures.

Boston Medical and Surgical Journal

"The illustrations are arranged in such a way as to illustrate all the common and many of the rare cardiac lesions, and the accompanying descriptive text constitutes a fairly continuous didactic treatise."

McConnell's Pathology

A Manual of Pathology. By GUTHRIE MCCONNELL, M. D., Assistant Surgeon, Medical Reserve Corps, U. S. Navy. 12mo of 523 pages, with 170 illustrations. Flexible leather, \$2.50 net.

NEW (2d) EDITION

Dr. McConnell has discussed his subject with a clearness and precision of style that make the work of great assistance to both student and practitioner. The illustrations have been introduced for their practical value.

New York State Journal of Medicine

"The book treats the subject of pathology with a thoroughness lacking in many works of greater pretension. The illustrations—many of them original—are profuse and of exceptional excellence."

McConnell's Pathology and Bacteriology

For Dental Students

Pathology and Bacteriology for Dental Students. By GUTHRIE MCCONNELL, M. D., Assistant Surgeon, Medical Reserve Corps, U. S. N. 12mo of 309 pages, illustrated. Cloth, \$2.25 net.

JUST ISSUED

This work is written expressly for dentists and dental students, emphasizing throughout the application of pathology and bacteriology in dental study and practice. There are chapters on disorders of metabolism and circulation; retrogressive processes, cell division inflammation and regeneration, granulomas, progressive processes, tumors, special mouth pathology, sterilization and disinfection, bacteriologic methods, specific micro-organisms, infection and immunity, and laboratory technic.

Dürck and Hektoen's Special Pathologic Histology

Atlas and Epitome of Special Pathologic Histology. By DR. H. DÜRCK, of Munich. Edited, with additions, by LUDVIG HEKTOEN, M. D., Professor of Pathology, Rush Medical College, Chicago. In two parts. Part I.—Circulatory, Respiratory, and Gastro-intestinal Tracts. 120 colored figures on 62 plates, and 158 pages of text. Part II.—Liver, Urinary and Sexual Organs, Nervous System, Skin, Muscles, and Bones. 123 colored figures on 60 plates, and 192 pages of text. Per part: Cloth, \$3.00 net. *In Saunders' Hand-Atlas Series.*

The great value of these plates is that they represent in the exact colors the effect of the stains, which is of such great importance for the differentiation of tissue. The text portion of the book is admirable, and, while brief, it is entirely satisfactory in that the leading facts are stated, and so stated that the reader feels he has grasped the subject extensively.

William H. Welch, M. D.,

Professor of Pathology, Johns Hopkins University, Baltimore.

"I consider Dürck's 'Atlas of Special Pathologic Histology,' edited by Hektoen, a very useful book for students and others. The plates are admirable."

Sobotta and Huber's Human Histology

Atlas and Epitome of Human Histology. By PRIVATDOCENT DR. J. SOBOTTA, of Würzburg. Edited, with additions, by G. CARL HUBER, M. D., Professor of Histology and Embryology in the University of Michigan, Ann Arbor. With 214 colored figures on 80 plates, 68 text-illustrations, and 248 pages of text. Cloth, \$4.50 net. *In Saunders' Hand-Atlas Series.*

INCLUDING MICROSCOPIC ANATOMY

The work combines an abundance of well-chosen and most accurate illustrations, with a concise text, and in such a manner as to make it both atlas and text-book. The great majority of the illustrations were made from sections prepared from human tissues, and always from fresh and in every respect normal specimens. The colored lithographic plates have been produced with the aid of over thirty colors.

Boston Medical and Surgical Journal

"In color and proportion they are characterized by gratifying accuracy and lithographic beauty."

Bosanquet on Spirochaetes

Spirochaetes: A Review of Recent Work, with Some Original Observations. By W. CECIL BOSANQUET, M.D., Fellow of the Royal College of Physicians, London. Octavo of 152 pages, illustrated. \$2.50 net.

ILLUSTRATED

This is a complete and authoritative monograph on the spirochaetes, giving morphology, pathogenesis, classification, staining, etc. Pseudospirochaetes are also considered, and the entire text well illustrated. The high standing of Dr. Bosanquet in this field of study makes this new work particularly valuable.

Levy and Klemperer's Clinical Bacteriology

The Elements of Clinical Bacteriology. By Drs. ERNST LEVY and FELIX KLEMPERER, of the University of Strasburg. Translated and edited by AUGUSTUS A. ESHNER, M. D., Professor of Clinical Medicine, Philadelphia Polyclinic. Octavo volume of 440 pages, fully illustrated. Cloth, \$2.50 net.

S. Solis-Cohen, M. D.,

Professor of Clinical Medicine, Jefferson Medical College, Philadelphia.

"I consider it an excellent book. I have recommended it in speaking to my students."

Lehmann, Neumann, and Weaver's Bacteriology

Atlas and Epitome of Bacteriology: INCLUDING A TEXT-BOOK OF SPECIAL BACTERIOLOGIC DIAGNOSIS. By PROF. DR. K. B. LEHMANN and DR. R. O. NEUMANN, of Würzburg. *From the Second Revised and Enlarged German Edition.* Edited, with additions, by G. H. WEAVER, M. D., Assistant Professor of Pathology and Bacteriology, Rush Medical College, Chicago. In two parts. Part I.—632 colored figures on 69 lithographic plates. Part II.—511 pages of text, illustrated. Per part: Cloth, \$2.50 net. *In Saunders' Hand-Atlas Series.*

Durck and Hektoen's General Pathologic Histology

ATLAS AND EPITOME OF GENERAL PATHOLOGIC HISTOLOGY. By PR. DR. H. DURCK, of Munich. Edited, with additions, by LUDVIG HEKTOEN, M. D., Professor of Pathology in Rush Medical College, Chicago. 172 colored figures on 77 lithographic plates, 36 text-cuts, many in colors, and 353 pages. Cloth, \$5.00 net. *In Saunders' Hand-Atlas Series.*

American Text-Book of Physiology

Second Edition

AMERICAN TEXT-BOOK OF PHYSIOLOGY. In two volumes. Edited by WILLIAM H. HOWELL, PH. D., M. D., Professor of Physiology in the Johns Hopkins University, Baltimore, Md. Two royal octavos of about 600 pages each, illustrated. Per volume: Cloth, \$3.00 net; Half Morocco, \$4.25 net.

"The work will stand as a work of reference on physiology. To him who desires to know the status of modern physiology, who expects to obtain suggestions as to further physiologic inquiry, we know of none in English which so eminently meets such a demand."—*The Medical News.*

Warren's Pathology and Therapeutics

Second Edition

SURGICAL PATHOLOGY AND THERAPEUTICS. By JOHN COLLINS WARREN, M. D., LL. D., F. R. C. S. (Hon.), Professor of Surgery, Harvard Medical School. Octavo, 873 pages, 136 relief and lithographic illustrations, 33 in colors. With an Appendix on Scientific Aids to Surgical Diagnosis and a series of articles on Regional Bacteriology. Cloth, \$5.00 net; Half Morocco, \$6.50 net.

Gorham's Bacteriology

A LABORATORY COURSE IN BACTERIOLOGY. For the Use of Medical, Agricultural, and Industrial Students. By FREDERIC P. GORHAM, A. M., Associate Professor of Biology in Brown University, Providence, R. I., etc. 12mo of 192 pages, with 97 illustrations. Cloth, \$1.25 net.

"One of the best students' laboratory guides to the study of bacteriology on the market. . . . The technic is thoroughly modern and amply sufficient for all practical purposes."—*American Journal of the Medical Sciences.*

Raymond's Physiology

New (3d) Edition

HUMAN PHYSIOLOGY. By JOSEPH H. RAYMOND, A. M., M. D., Professor of Physiology and Hygiene, Long Island College Hospital, New York. Octavo of 685 pages, with 444 illustrations. Cloth, \$3.50 net.

"The book is well gotten up and well printed, and may be regarded as a trustworthy guide for the student and a useful work of reference for the general practitioner. The illustrations are numerous and are well executed."—*The Lancet*, London.

Ball's Bacteriology

Seventh Edition, Revised

ESSENTIALS OF BACTERIOLOGY: being a concise and systematic introduction to the Study of Micro-organisms. By M. V. BALL, M. D., Late Bacteriologist to St. Agnes' Hospital, Philadelphia. 12mo of 289 pages, with 135 illustrations, some in colors. Cloth, \$1.00 net. *In Saunders' Question-Compend Series.*

"The technic with regard to media, staining, mounting, and the like is culled from the latest authoritative works."—*The Medical Times*, New York.

Budgett's Physiology

New (3d) Edition

ESSENTIALS OF PHYSIOLOGY. Prepared especially for Students of Medicine, and arranged with questions following each chapter. By SIDNEY P. BUDGETT, M. D., formerly Professor of Physiology, Washington University, St. Louis. Revised by HAVAN EMERSON, M. D., Demonstrator of Physiology, Columbia University. 12mo volume of 250 pages, illustrated. Cloth, \$1.00 net. *Saunders' Question-Compend Series.*

"He has an excellent conception of his subject. . . It is one of the most satisfactory books of this class"—*University of Pennsylvania Medical Bulletin.*

Leroy's Histology

New (4th) Edition

ESSENTIALS OF HISTOLOGY. By LOUIS LEROY, M. D., Professor of Histology and Pathology, Vanderbilt University, Nashville, Tennessee. 12mo, 263 pages, with 92 original illustrations. Cloth, \$1.00 net. *In Saunders' Question-Compend Series.*

"The work in its present form stands as a model of what a student's aid should be; and we unhesitatingly say that the practitioner as well would find a glance through the book of lasting benefit."—*The Medical World*, Philadelphia.

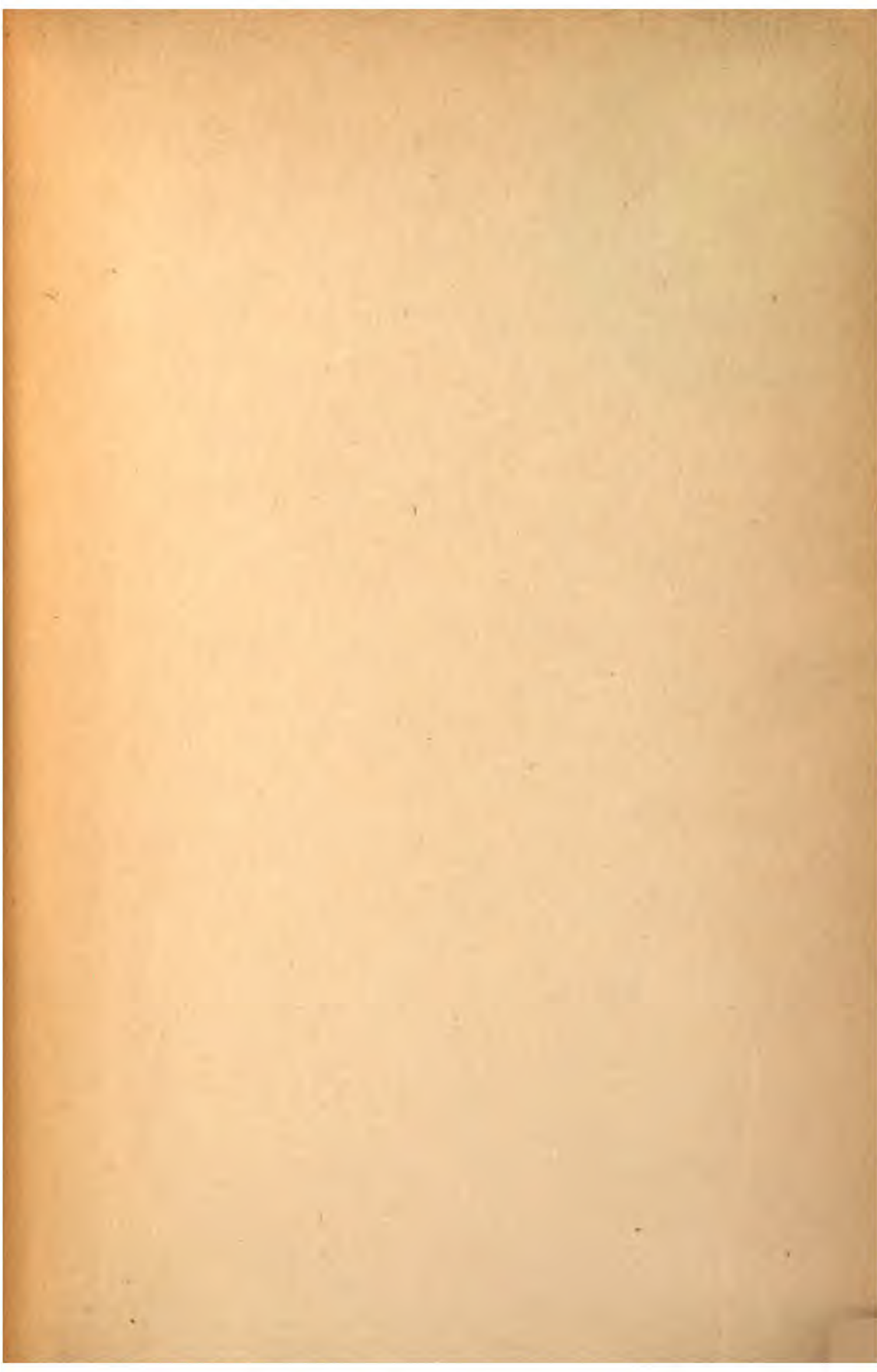
Barton and Wells' Medical Thesaurus

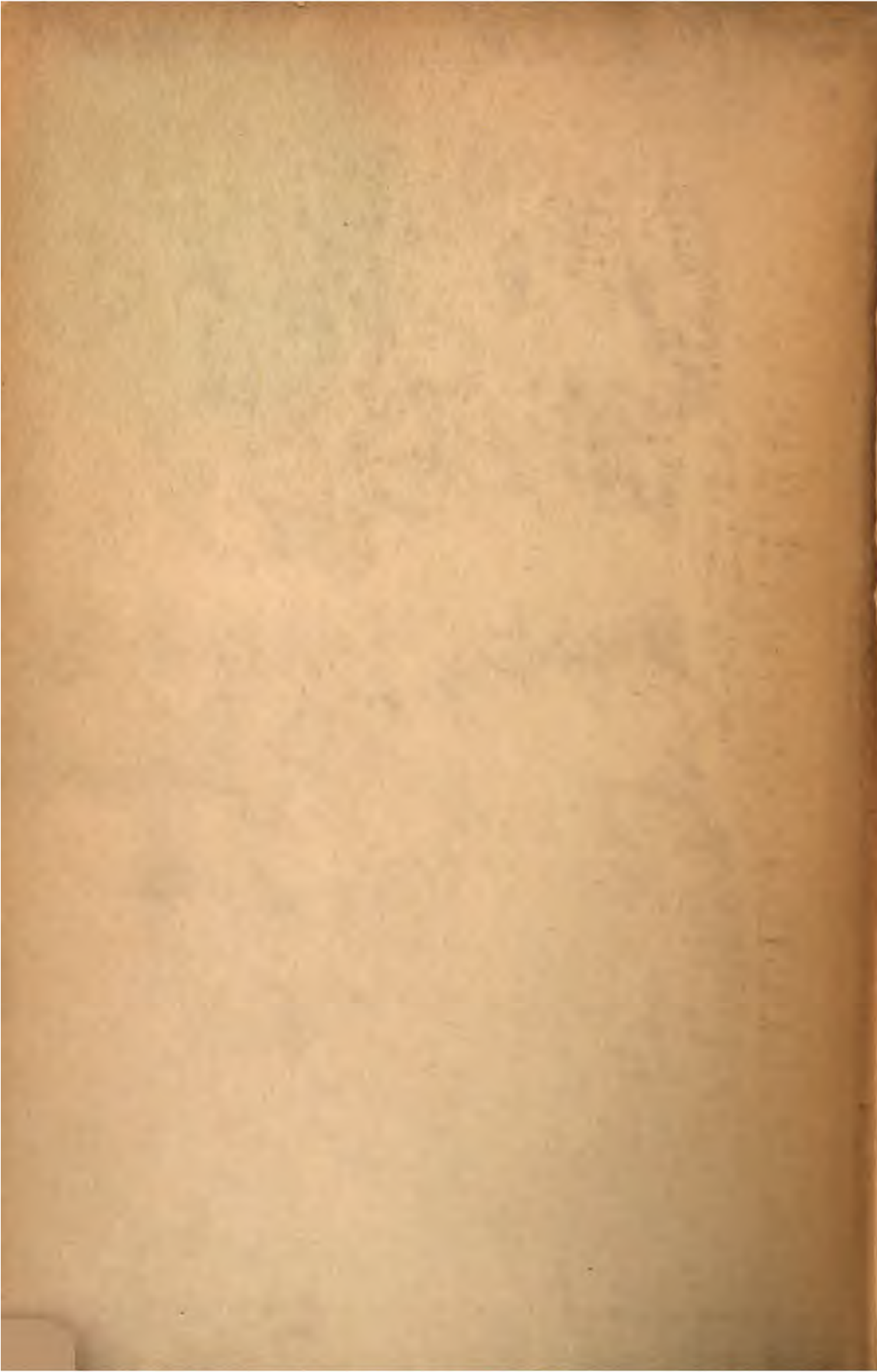
A THESAURUS OF MEDICAL WORDS AND PHRASES. By WILFRED M. BARTON, M. D., Assistant Professor of Materia Medica and Therapeutics, and WALTER A. WELLS, M.D., Demonstrator of Laryngology, Georgetown University, Washington, D. C. 12mo, 534 pages. Flexible leather, \$2.50 net; thumb indexed, \$3.00 net.

American Pocket Medical DictionaryJust Out
New (9th) Edition

AMERICAN POCKET MEDICAL DICTIONARY. Edited by W. A. NEWMAN DORLAND, M. D., Editor "American Illustrated Medical Dictionary." Containing the pronunciation and definition of the principal words used in medicine and kindred sciences, with 75 extensive tables. 693 pages. Flexible leather, with gold edges, \$1.00 net; with patent thumb index, \$1.25 net.

"I can recommend it to our students without reserve."—J. H. HOLLAND, M. D., of the *Jefferson Medical College*, Philadelphia.





COUNTWAY LIBRARY



HC 2LY2 2

8.A.293.

A text-book of pathology, 1915

Countway Library

BDZ2259



3 2044 045 598 083

8.A.293.

A text-book of pathology, 1915

Countway Library

BDZ2259



3 2044 045 598 083